No. 22-1877

IN THE
United States Court of Appeals
FOR THE FEDERAL CIRCUIT

EDWARDS LIFESCIENCES CORPORATION, EDWARDS LIFESCIENCES LLC,

Plaintiffs- Appellants,

v.

MERIL LIFE SCIENCES PVT. LTD., MERIL, INC.

Defendants – Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA
CASE NO. 4:19-CV-06593-HSG

CORRECTED OPENING BRIEF AND ADDENDUM OF APPELANTS EDWARDS LIFESCIENCES CORPORATION AND EDWARDS LIFESCIENCES LLC

Steven M. Hanle, *Principal Attorney*
STRADLING YOCCA CARLSON & RAUTH PC
660 Newport Center Drive, Suite 1600
Newport Beach, CA 92660-6422
(949) 725-4000

Christy G. Lea
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street, 14th Floor
Irvine, CA 92614
(949) 760-0404

Carlo Van den Bosch
Gazal Pour-Moezzi
SHEPPARD MULLIN RICHTER & HAMPTON LLP
650 Town Center Dr., 10th Floor
Costa Mesa, CA 92626
(714) 513-5100

Attorneys for Plaintiffs - Appellants Edwards Lifesciences Corporation and Edwards Lifesciences LLC

November 7, 2022

PATENT CLAIMS AT ISSUE

There are no patent claims at issue on this appeal.

CERTIFICATE OF INTEREST

Counsel for Plaintiffs-Appellants Edwards Lifesciences Corporation and Edwards Lifesciences LLC certify the following:

1. The full name of every party represented by me is: Edwards Lifesciences Corporation, Edwards Lifesciences LLC

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is: None.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are: None.

4. The name of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

Stradling Yocca Carlson & Rauth, P.C.: Matthew Robert Stephens*
Sheppard Mullin Richter & Hampton LLP: Michelle LaVoie Wisniewski, and Anne-Marie D. Dao
Knobbe Martens Olson & Bear LLP: Brian C. Horne, Ioanna Sophia Bouris, and Adam Rolando Aquino*

*No longer with the firm.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal: None.

6. Information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees): None.

Dated: November 7, 2022

By: */s/ Christy G. Lea*
Christy G. Lea

Attorney for Plaintiffs-Appellants
Edwards Lifesciences Corporation and
Edwards Lifesciences LLC

TABLE OF CONTENTS

Page No.

TABLE OF CONTENTS
(*cont'd*)

Page No.

TABLE OF AUTHORITIES

Page No(s).

TABLE OF AUTHORITIES
(*cont'd*)

Page No(s).

TABLE OF AUTHORITIES
(*cont'd*)

Page No(s).

OTHER AUTHORITIES

STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5(a), no other appeal in or from the same civil action in the lower court was previously before this or any other appellate court.

Pursuant to Federal Circuit Rule 47.5(b), counsel is unaware of any other pending cases that will directly affect, or will be directly affected by, the Court's decision in this appeal.

JURISDICTIONAL STATEMENT

The district court had jurisdiction in this patent infringement case under 28 U.S.C. §§ 1331 and 1338. This Court has jurisdiction over this appeal pursuant to 28 U.S.C. § 1295(a)(1).

On May 18, 2022, the district court entered final judgment after previously dismissing Edwards' patent infringement claims on summary judgment. Edwards timely filed its notice of appeal on June 1, 2022.

STATEMENT OF THE ISSUES

Whether the district court erred in granting summary judgment that Meril's alleged patent infringement for importing medical devices for use at a commercial industry conference was exempt under the safe-harbor provision of 35 U.S.C. § 271(e)(1) where:

(a) the district court erroneously failed to credit contemporaneous evidence creating a triable issue of fact as to whether Meril imported the devices solely for uses reasonably related to U.S. FDA submissions,

(b) the district court erroneously failed to draw reasonable inferences in favor of the non-movant Edwards, relying instead on self-serving and uncorroborated declarations from Meril employees who lacked personal knowledge of the material facts declared, and

(c) while purporting to apply an objective standard to determine whether Meril imported the devices solely for uses reasonably related to U.S. FDA submissions, the district court erroneously relied on Meril's alleged purpose for the importation?

STATEMENT OF THE CASE

Edwards filed its Complaint in the United States District Court for the Northern District of California on October 14, 2019, alleging Meril infringed three of Edwards' patents: U.S. Patent Nos. 10,292,817, 9,393,110, and 9,119,716. Appx27-28. The '817 patent relates to methods of making implantable prosthetic heart valves. Appx84-110. The '110 patent relates to an assembly for implanting the heart valves, including a delivery device and prosthetic heart valve. Appx111-152. The '716 patent relates to a delivery device for implanting a prosthetic heart valve. Appx153-189. Edwards alleged that Meril infringed the '817 patent under 35 U.S.C. § 271(g) and the '110 and '716 patents under 35 U.S.C. § 271(a) by importing its Myval heart valve and delivery system (the "Myval Devices") into the United States.

Meril moved to dismiss the patent infringement causes of action, arguing that its importation was protected by the safe harbor of 35 U.S.C. § 271(e)(1). *See* Appx29-30; Appx208-214. Section 271(e)(1) provides that "[i]t shall not be an act of infringement to . . . import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates" drugs or medical devices. Meril alleged that it imported the Myval Devices for display at a medical conference in order to recruit clinical investigators to perform clinical studies. On February 18, 2020, the district court denied Meril's motion. Appx208-214. In denying Meril's motion to

dismiss, the Court held that "[n]ot all activities performed prior to FDA approval" fall within the safe harbor exemption. Appx211 (citing *Amgen Inc. v. Int'l Trade Comm'n*, 565 F.3d 846, 852 (Fed. Cir. 2009) (*Amgen I*) (question of fact as to whether safe harbor applies where evidence suggests that some studies were conducted at the request of the marketing department for brand recognition purposes)). The district court also held that "commercial intent" may be probative of whether an otherwise infringing act is "solely for uses reasonably related" to a regulatory submission. Appx213 (citing *Amgen Inc. v. Hospira, Inc.*, 944 F.3d 1327, 1340 (Fed. Cir. 2019) (*Amgen II*) (upholding jury's finding that manufacturing of batches for commercial inventory was not exempt under Section 271(e)(1)).

On April 6, 2020, Edwards filed a First Amended Complaint alleging infringement of two additional patents: U.S. Patent Nos. 6,878,168 and 10,053,256. Appx215-252. Both patents relate to methods of treating bioprosthetic tissues used in heart valves to mitigate post-implantation calcification. Appx190-198; Appx199-207. Edwards alleged that Meril infringed both patents under 35 U.S.C. § 271(g) by importing its Myval heart valve into the United States. Appx246-247.

Shortly thereafter, Meril moved for summary judgment based on its § 271(e) safe harbor defense. Appx272-293. Meril again claimed, through declarations, that it imported the accused devices to use at a U.S. medical conference for the

purpose of recruiting investigators (physicians) to perform clinical studies, allegedly for submitting data to the United States Food and Drug Administration ("FDA"). Appx294-296; Appx369-374. Edwards submitted contemporaneous evidence that contradicted Meril's alleged purpose and use, including: (a) evidence that Meril imported the Myval Devices solely for use as commercial sales tools at a trade show, unrelated to any clinical or regulatory efforts; and (b) evidence that the clinical study planned by Meril at the time of importation was a post-approval European study that was unrelated to FDA submissions. *See* Appx568-592. Nonetheless, on October 16, 2020, the district court granted Meril's motion for summary judgment of no infringement based on the safe harbor exemption. Appx1-20. Following a settlement on all other causes of action in the case, the district court entered final judgment on the patent infringement claims on May 18, 2022. Appx21-22.

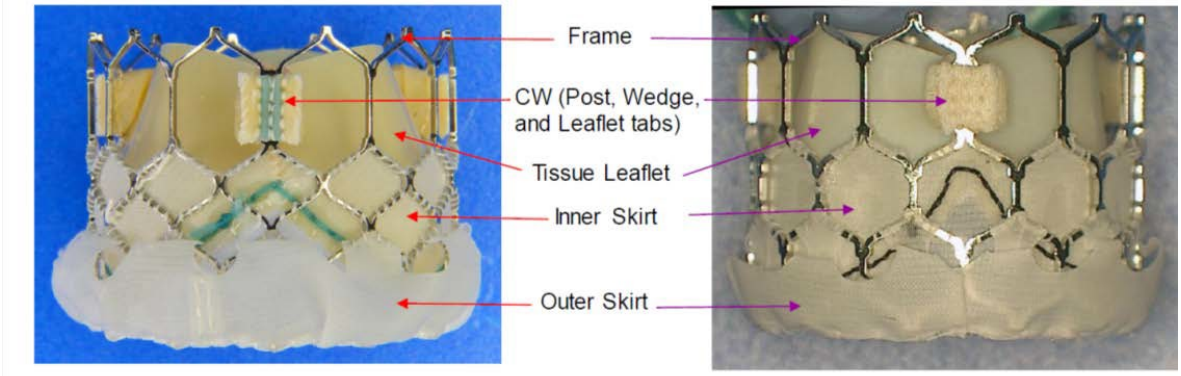
Edwards now appeals the district court's grant of summary judgment on Meril's § 271(e)(1) safe harbor defense.

STATEMENT OF FACTS

Edwards is a leading innovator and supplier of medical devices for the treatment of heart disease and is world renowned for its artificial heart valves. Among its best-known products are its line of SAPIEN® transcatheter prosthetic heart valves and related delivery systems. Edwards revolutionized the industry when it developed and commercialized a prosthetic heart valve that could be delivered via catheter while the heart is still beating. Edwards' innovations have saved hundreds of thousands of patients from having to undergo traumatic open-heart surgery, which requires stopping the patient's heart and placing the patient on a heart-lung machine to keep them alive during the procedure.

Meril attempted to capitalize on Edwards' innovation and success by copying the SAPIEN product design. Appx222-225. Meril's transcatheter heart valve, which it calls "Myval," is nearly identical to Edwards' SAPIEN valve:

Edwards SAPIEN 3 **Meril Myval**



Id. Meril makes its Myval transcatheter heart valve and the accompanying Navigator delivery system (collectively "Myval Devices") in India. Appx370. Edwards brought this lawsuit to enforce its patent rights and protect its innovation in the SAPIEN valves.

On September 24, 2019, Meril imported two Myval Devices into the United States and to San Francisco where the Transcatheter Cardiovascular Therapeutics Conference ("TCT Conference") was scheduled to begin on September 25, 2019. Appx372. Two days after the conference had begun, on September 27, 2019, a Meril employee named Nilay Lad carried the Myval Devices to the convention hall at the TCT Conference. Appx370, Appx373-374. Meril claims that it never removed the Myval Devices from the bag in which they were transported and that it never showed the Myval Devices to any conference attendees. Appx374. On September 28, 2019, Mr. Lad handed the bag containing the Myval Devices to another Meril employee named Sanjeev Bhatt who transported them to Europe. Appx374; Appx295-296.

In moving for summary judgment under the safe harbor statute, Meril relied on declarations from those two employees, Nilay Lad and Sanjeev Bhatt. Appx369-374; Appx294-296. Lad declared that Meril imported the Myval Devices for display at the 2019 TCT Conference, where Meril allegedly intended "to recruit clinical researchers for the clinical studies that would be necessary for FDA approval" of the Myval Devices. Appx371; Appx296. However, the

contemporaneous evidence discussed below contradicts that claim, and supports the conclusion that Meril imported the Myval Devices solely as a commercial sales tool. Moreover, the evidence supports the conclusion that the clinical study that Meril references as part of its defense was a post-approval European study that was unrelated to FDA approval.

I. THE MYVAL DEVICES HAD ALREADY RECEIVED REGULATORY APPROVAL IN EUROPE BEFORE THEY WERE IMPORTED INTO THE UNITED STATES

Meril began clinical trials for the Myval Devices in India in June 2017 and received regulatory approval for the Indian market on October 31, 2018. Appx370. As is typical with clinical trials for regulatory approval, Meril conducted a single-arm clinical trial called Myval-1 in Indian hospitals. Appx657; Appx335. A single-arm clinical trial is one involving a single device, without any comparison to other devices. Appx452. Based on that same single-arm clinical trial, the Myval Devices received CE certification in April of 2019, which allowed Meril to market and sell the Myval Devices for use in Europe. Appx370. Thus, by the time Meril imported the Myval Devices for the TCT Conference in September 2019, they had already been approved for use by physicians in Europe. *Id.*

II. MERIL IMPORTED THE MYVAL DEVICES TO THE TCT CONFERENCE AS COMMERCIAL SALES AND MARKETING TOOLS

The TCT Conference is the leading conference in the field of interventional cardiology. With over 11,500 attendees, including thousands of physicians from

Europe and other countries outside the United States (Appx735-737), TCT provides companies with "unparalleled marketing opportunities" to "increase visibility of products and services":

Appx730. The 2019 TCT Conference was held in San Francisco from September 25 to September 29. Appx729.

Meril took advantage of the TCT marketing opportunities. It sent "invitations" drafted by Meril's marketing personnel to over 3,000 TCT registrants prior to the Conference, encouraging them to visit Meril's tradeshow booth at TCT and "Experience Meril's technologies & hands-on simulation of Meril's TAVR system — Myval THV." Appx884-886; Appx888; Appx616. As shown below, the invitation did not mention any purported need for, or recruitment of, clinical investigators:

Appx885.

Meril also engaged in other marketing efforts for Myval leading up to TCT. On September 14, 2019, Meril sent an email blast to thousands of physicians and industry professionals registered to receive such communications regarding TCT 2019, including hundreds based in Europe. Appx670; Appx889-893; Appx570; Appx745-748. Like Meril's earlier marketing invitation, it too invited recipients to "have hands-on and VR sessions on Meril's TAVR system – Myval™ THV." Appx747; Appx890-892. This email blast touted the Myval Devices as "ensuring

predictable clinical safety and efficacy outcomes," and did not mention anything about clinical trials or recruiting clinical investigators:

Appx746-748. In contrast, less than two months later, Meril sent an e-blast to attendees of the London Valves conference in Europe, in which it expressly advertised "9 Landmark Trial investigator meetings." Appx964-965.

Meril's marketing materials also advertised to thousands of TCT attendees that Myval was "CE Approved," meaning it could be sold commercially in Europe. Appx570; Appx745-47; Appx889-891. Meril also updated its Myval brochure specifically for the TCT conference, again touting its CE Approval and even providing "Myval – THV Ordering Information." Appx825-826, Appx852.

In furtherance of its plan to sell Myval Devices to European physicians at the TCT Conference, Meril executives, in consultation with its lawyers, drafted and announced "Instructions for TCT 2019 for Myval THV System" to its twenty employees who attended TCT. Appx632; Appx907-909. With respect to the Myval Devices imported to TCT, Meril instructed its employees at TCT as follows:

- "Do not make any sales or offers for sale at the conference, or while in the United States for the US market. **You can make offer for other countries**." (Emphasis added.)
- "Do not carry too many demo units."

Id. Meril employees were thus encouraged to make offers to sell Myval Devices for commercial use in other countries where Myval Devices were approved. The Instructions also refer to the imported Myval Devices as "demo units," which indicates that they were to be used as commercial sales tools by Meril's salesforce—not as recruiting tools by its clinical trial team. See *infra* Statement of Facts § III. The relatively few Myval demo units thus supported Meril's sales efforts to hundreds, if not thousands, of physicians from "other countries." Appx909; Appx735-737. The Instructions for Myval also stated: "If possible, refer discussions of pricing, delivery, and other commercial topics to representatives outside the US for the US market." Appx909. Most importantly, Meril's Instructions, like its invitation, email blast and brochure, did not mention a single word about recruiting clinical investigators at TCT. Appx907-909; Appx882; Appx884-886; Appx890-893; Appx746-748; Appx825-853.

Moreover, Mr. Lad testified that it was Meril's marketing team that decided they would do hands-on sessions with the Myval Devices using a simulator. Appx640. Mr. Lad, an employee with no regulatory or other responsibilities relating to Myval, brought the Myval Devices to the conference on September 27, where the purported plan was for marketing personnel to demonstrate them with a simulator. Appx612-613, Appx640; Appx373-374. The demonstrations were not to be limited to any particular persons, and "anybody who wants to come can do the hands-on session." Appx640. However, according to Meril's witnesses, Meril

never displayed the Myval Devices at TCT because the simulator malfunctioned. Appx374. Meril then allegedly opted not to show the Myval Devices without the simulator, even though it had shown the Myval Devices, without a simulator, at previous conferences. Appx570; Appx874-879; Appx614-615; Appx618-619.

III. THE IMPORTATION OF MYVAL DEVICES WAS UNRELATED TO ANY RECRUITING OF CLINICAL INVESTIGATORS

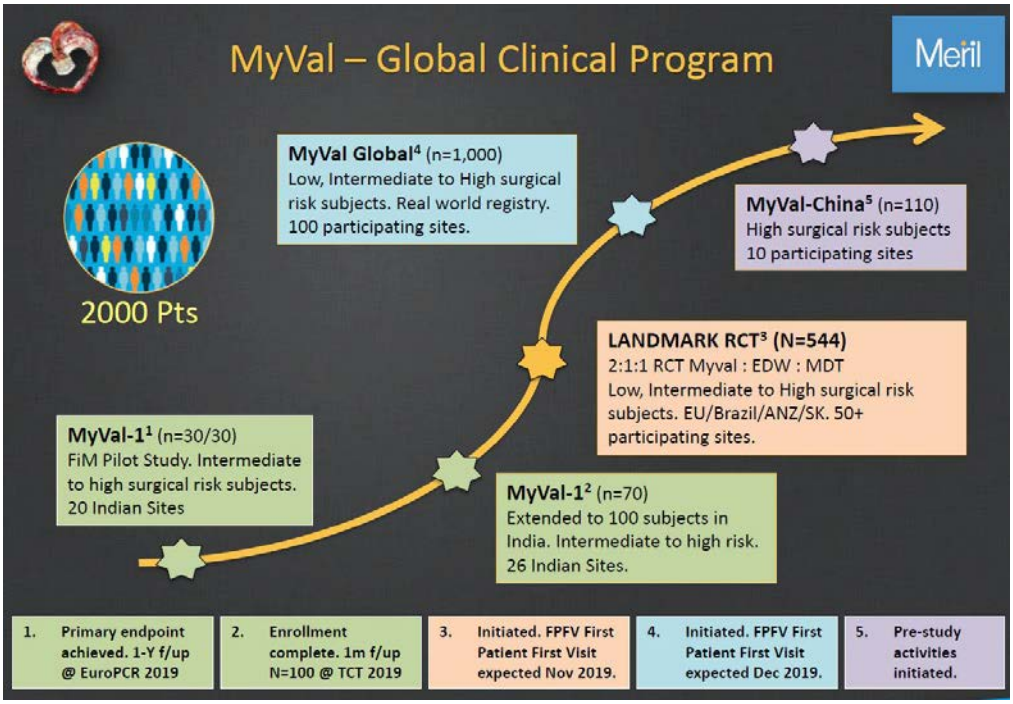
On the evening of September 26, 2019, Meril held a dinner at a restaurant for prospective clinical investigators for its Landmark Trial. Appx618; Appx647. It was the only meeting Meril held for clinical investigators at TCT 2019. Appx647. Oddly, despite claiming that it imported the Myval Devices to recruit clinical investigators, Meril never even planned to bring them to this meeting, and did not do so. Appx618. In fact, Meril's communications regarding this meeting never mention any sample Myval Devices or hands-on sessions with Myval. Appx571; Appx961; Appx774-783.

In sum, while contemporaneous documentary evidence shows that Meril's importation of the Myval Devices was to support commercial sales efforts, no contemporaneous evidence ties the importation to the recruitment of clinical investigators, let alone clinical investigators for a study relating to FDA submissions.

IV. MERIL PLANNED TO COMPARE THE MYVAL DEVICES WITH OTHER LEADING DEVICES IN EUROPE TO BOOST COMMERICAL SALES

Shortly after receiving CE-mark regulatory approval in Europe in April 2019, Meril announced plans to conduct its "Landmark" Trial, a post-approval comparative clinical trial in Europe. Appx298, 334 (Myval – Global Clinical Program as of March 30, 2019; Appx588-589; Appx912 (Myval – Global Clinical Program as of May 2019). Meril sought to compare Myval with the market leading devices in Europe: Edwards' SAPIEN valves and Medtronic's CoreValve Evolut valves. Appx657. A Meril brochure seized in May 2019 at the EuroPCR industry conference in France included a slide on Meril's "Myval – Global Clinical Program," including the planned Landmark Trial. Appx588-589; Appx912.[1] As shown, the Landmark Trial was to include clinical sites in the EU, Brazil, Australia/New Zealand, and South Korea, but **not the United States**.

[1] The seizure was the result of a proceeding in France alleging that the Myval Devices infringed Edwards' European patents. Appx613.



Appx912. At the time it planned the Landmark Trial as an outside-the-U.S. ("OUS") study, Meril knew FDA approval would require U.S. trial sites. Appx677; Appx716. Thus, the Landmark Trial was never an "FDA clinical trial" as claimed by Meril. Appx372-373 (Lad Decl. ¶¶ 12, 15).

In a brochure published in August 2020, long after Meril imported the Myval Devices to the TCT Conference in the United States, Meril continued to present the Landmark Trial as a comparative, three-arm trial to be conducted entirely outside the United States, starting in late 2020. Appx591; Appx915. Thus, Meril planned its Landmark Trial after the Myval Devices were approved in Europe in April 2019, and never planned to include U.S. clinical sites in that post-approval trial. Moreover, no contemporaneous evidence shows any communications with U.S. clinical investigators or clinical sites resulting from

Meril's purported "recruiting" efforts at TCT. Appx709; Appx961; Appx774-783; Appx1218.

V. MERIL'S RECRUITMENT OF CLINICAL INVESTIGATORS IN EUROPE DID NOT INCLUDE DEMONSTRATING THE MYVAL DEVICES

Meril began marketing its Myval Devices for sale in Europe after CE approval in April 2019. Appx370. In addition, Meril's Senior Vice President, Sanjeev Bhatt, traveled around Europe recruiting clinical investigators for the Landmark Trial. Appx569; Appx719, 721-727. Bhatt's primary recruitment tools were PowerPoint presentations. He testified that "[t]he slide deck is the most meaningful way to have a conversation with a clinician. It's the best thing that you can do." Appx669. Notably, Bhatt admitted that he tries to avoid using sample devices when recruiting clinical investigators, and he never used a simulator to demonstrate a sample device to recruit an investigator. *Id.* Bhatt's admission further supports that Meril imported the Myval Devices not for use in recruiting clinical investigators but for use as sales tools for its TCT marketing team. Appx884-886; Appx616; Appx890-892; Appx372; Appx397-399; Appx907-909.

VI. MERIL'S PRESENTATIONS ON THE LANDMARK TRIAL CONFIRM IT WAS TO TAKE PLACE OUTSIDE THE UNITED STATES

Meril's claim that it planned to recruit U.S. clinical investigators at TCT 2019 for the Landmark Trial is contradicted by a wealth of contemporaneous evidence. Meril's own TCT presentation reported that the Landmark Trial was to

be conducted entirely outside the United States. Appx675; Appx923, 946, 953. Later presentations, such as one dated November 17, 2019, also reported the Landmark trial as an OUS study. Appx969, 996-997. Indeed, the brochure on Meril's website as of August 3, 2020 (which was continually updated) advertised the Landmark Trial as an OUS study with 50+ sites in Europe, Australia, and New Zealand. Appx591; Appx915-916. It acknowledged that the first patient would not be enrolled in the trial until late 2020, at the earliest. *Id*. The evidence thus supports the conclusion that the Landmark Trial was not reasonably related to FDA regulatory approval, which Meril knew would require U.S. trial sites. Appx677; Appx716.

VII. THE IMPORTATION OF MYVAL DEVICES WAS UNRELATED TO MERIL'S VOLUNTARY "PRESUBMISSION" TO THE FDA

On August 23, 2019, a few months after the seizure at a European conference, Meril consulted attorneys about importing Myval Devices to the September 2019 TCT Conference in the United States. Appx610-612; Appx869-873. From late August to early September, Meril consulted three different sets of attorneys regarding the importation of Myval Devices for use at TCT 2019. *Id*.

After starting those attorney consultations, Meril began communicating with the FDA and with a regulatory consulting firm called CardioMed. On September 3, 2019, Meril inquired about the clinical data needed for an FDA presubmission. Appx388. On September 5, 2019, Meril informed CardioMed that it was planning

an OUS study (the Landmark Trial) with no plans for any investigation sites in the United States. Appx1021-1022. Meril also sent a general email inquiry to the FDA mentioning its planned OUS study and asking about the requirements for a "Pre-submission." Appx1015-1019. On September 9, 2019, the FDA responded to Meril's general inquiry that pre-submissions are entirely voluntary and merely used to get FDA feedback on planned studies. Appx1015.

On September 23, 2019, long after Meril advertised that it would demonstrate Myval Devices at TCT, CardioMed advised Meril that the FDA requires clinical trial sites in the United States, and would not approve a heart valve based on an OUS study. Appx1025-1026; Appx1029-1030. CardioMed recommended that Meril propose two studies: its OUS (Landmark) study and a separate single arm study in the United States, but cautioned that Meril could only perform a domestic study after receiving an Investigational Device Exemption (IDE). Appx1026; Appx1032. No evidence suggests that Meril has ever attempted to obtain an IDE from the FDA regarding the Myval Devices. Rather, Meril admitted that it was nowhere near applying for the IDE, and did not have a single U.S. investigation site lined up. Appx676-677, 691-692. At the time of its importation of Myval Devices for TCT in September 2019, Meril had only engaged in exploratory communications with the FDA and its consultant regarding a presubmission.

On November 9, 2019, weeks after TCT, Meril informed CardioMed that it was changing its clinical study strategy. Appx1036-1037. Rather than pursuing the recommended two-study strategy, Meril would propose only its Landmark study but would propose to include both OUS and domestic sites, with one third of the study subjects in the United States. *Id.* CardioMed immediately advised that the FDA would not accept a study design with less than 50-60% U.S. enrollment and it did not want to risk its reputation signing a presubmission seeking guidance on such a study. Appx1036; Appx1047; *see also* Appx677; Appx716 (acknowledging that Meril knew that the FDA would require a significant cohort of U.S. patients for any FDA clinical trial).

Meril ultimately filed its presubmission on December 4, 2019, months after the importation of Myval Devices for TCT. Appx374; Appx445-495. Against CardioMed's advice, Meril sought guidance on a proposed study with only one third of the subjects in the United States. Appx459. As expected, the FDA responded to Meril's voluntary presubmission that the proposed clinical study would not generate adequate evidence for the FDA because it included too few domestic patients. Appx1049-1050. There is no evidence that Meril ever submitted any filing required by the FDA for the approval of a medical device, such as an application for an IDE or premarket approval (PMA)—and certainly no

evidence of any such application submitted prior to TCT 2019. To the present day, the Landmark Trial does not include U.S. clinical investigators or study locations.[2]

VIII. THE DISTRICT COURT'S SUMMARY JUDGMENT ORDER

On October 16, 2020, the district court granted Meril's motion for summary judgment, holding that its importation of Myval Devices was exempt from patent infringement under the safe harbor of 35 U.S.C. § 271(e)(1). Appx1-20. The district court held that "the safe harbor inquiry focuses on acts or uses, and not on purposes, intent or motive." Appx7. It also held that the statute "extends even to activities the 'actual purpose' of which may be 'promotional' rather than regulatory, at least where those activities are 'consistent with the collection of data necessary for filing an application with the FDA.'" Appx7. The district court did not explain how its holding squares with § 271(e)(1), which requires that the infringing act be "**solely** for uses reasonably related to the development and submission of information under a Federal law." (Emphasis added.)

The district court also held that the statute, despite stating "solely for uses," does not require an "actual use." Appx8. The court held that as long as the infringing importation is "reasonably related to obtaining FDA approval," then the

[2] https://clinicaltrials.gov/ct2/show/NCT04275726?term=myval&draw=2&rank=2. *See, e g.*, *Bryant v. Carleson*, 444 F.2d 353, 357-58 (9th Cir. 1971) (taking judicial notice of developments since the appeal, including relevant administrative action of the Administrator of the United States Department of Health, Education and Welfare); *Kirby v. Pa. R.R. Co.*, 188 F.2d 793, 795 (3d Cir. 1951) (taking judicial notice of a paper describing the operation of the Railroad Adjustment Board, acknowledging that paper was "not in the record").

safe harbor applies. Appx8. The district court never explained how an importation could be deemed "reasonably related to obtaining FDA approval" without considering either the subjective intent of the importer or the importer's actual use of the device after importation.

Citing this Court, the district court held that "demonstrations at medical conferences are covered by the Section 271(e)(1) safe harbor" as a matter of law. Appx8. And because "transporting a device to a medical conference is a necessary and predicate act for displaying the device," the district court reasoned that importing the device for display at a medical conference is also exempt under the safe harbor, regardless of intended purpose or actual use. Appx9.

Crediting the testimony of Meril's witnesses, the district court found that "Meril had taken significant steps towards obtaining FDA approval." Appx9. It failed to credit Edwards' contrary evidence showing that, by the time of the importation, Meril had only engaged in exploratory communications regarding an entirely voluntary presubmission that was for guidance only, was not required for FDA approval, and did not even begin the FDA approval process. Appx1015-1019. Instead, the district court found that Meril's OUS Landmark trial was reasonably related to FDA approval, because FDA approval **can be** supported by clinical trials that include patients both within and outside the United States. Appx9, n3.

Throughout its Order, the district court repeatedly credited Meril's declarations and deposition testimony, even when contradicted by contemporaneous documents and when reasonable inferences could be drawn in favor of Edwards. The district court repeatedly stated that Edwards did not dispute Meril's facts, when the record shows otherwise. Edwards submitted 45 exhibits that disputed Meril's version of the facts. *See* Appx568-592. Edwards' brief contained entire sections disputing Meril's version of the facts, including:

> A. The Contemporaneous Evidence Shows that Meril's Importations Were Not for the Purpose of Recruiting Clinical Investigators for FDA Approval,
>
> C. The Landmark Trial Was Not an "FDA Clinical Trial," and
>
> D. After-the-Fact FDA Activities Cannot Manufacture a Safe Harbor Defense.

Appx556-560. The district court never addressed the documents submitted by Edwards and cited in these sections, nor did it draw all reasonable inferences from them in Edwards' favor as the non-movant.

Indeed, the district court placed heavy emphasis on its finding that Meril "did not sell or offer to sell" its Myval Devices at TCT 2019—a fact it called "undisputed." Appx4-5, 10, 15. But as explained above, that very fact was refuted by Meril's own documents submitted by Edwards in opposition to Meril's motion. *See, e.g.*, Appx907-909 ("You can make offer for other countries."). And the

separate infringing act of importation does not require a sale or offer to sell in any event.

The district court also held that Meril's purpose for importing the Myval Devices is irrelevant, but found that, if purpose were relevant, Meril's purpose was to support clinical trials to seek premarket approval from the FDA. Appx14. Again, the district court failed to address any of the numerous documents Edwards submitted showing that Meril's purpose for bringing the Myval Devices to TCT was solely to support commercial sales offers to European physicians, not to recruit clinical investigators for an FDA trial. *See* Appx14-15.

SUMMARY OF THE ARGUMENT

The district court erred in three respects when granting summary judgment in favor of Meril and holding that its importation of Myval Devices to TCT was within the safe harbor defense. First, in determining that the importation was solely for uses reasonably related to an FDA submission, the district court failed to view the evidence in the light most favorable to Edwards by ignoring substantial contemporaneous evidence from which a reasonable jury could conclude otherwise. The contemporaneous evidence supported a reasonable conclusion that Meril imported the Myval Devices solely for use as a commercial sales tool, and not for use in recruiting clinical investigators. This contemporaneous evidence includes:

- Marketing materials advertising the Myval Devices as "CE Approved" and inviting TCT attendees to "hands-on" demonstrations of the Myval Devices – without any mention of clinical trials or clinical investigators. Appx 372; Appx397-399; Appx570; Appx746-748; Appx881-882; Appx884-886; Appx890-893; Appx825-853.
- Instructions to Meril sales personnel attending TCT that they could use Myval "demo units" while offering to sell the Myval Devices for use outside the United States. Appx632; Appx907-909. Again, these Instructions, which are the most probative evidence of Meril's

planned use for the imported Myval Devices, never mention clinical trials or clinical investigators.

- Meril's admissions that it never planned to use the imported Myval Devices at its only investigator meeting at TCT, and that it rarely if ever used sample devices to recruit clinical investigators. Appx618; Appx669.

Even if the importation of Myval Devices were somehow related to the Landmark Trial, the district court compounded its error by also accepting Meril's argument that its Landmark Trial was reasonably related to FDA approval, despite contrary evidence that:

- The Landmark Trial was a post-EU-approval study to be conducted in Europe to compare the Myval Devices to the leading devices in the European market. *See* Appx9 n.3.[3]
- When Meril planned the Landmark Trial as an OUS trial, Meril knew FDA approval would require a trial with U.S. sites. Appx677; Appx716.

[3] As correctly noted by the district court, the Landmark Trial was primarily a European trial, but with a few sites in other foreign countries. Post-approval and foreign studies are not within the safe harbor absent "a clear indication that [foreign clinical] work was submitted, or to be submitted, to the FDA." *NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 208-209 (D.N.J. 1994) (foreign clinical work); *Amgen I*, 565 F. 3d at 852-53 (post-approval comparative studies).

- Meril first mentioned an FDA presubmission only after deciding to import Myval Devices to TCT and then consulting with its attorneys about the importation. Appx884-886; Appx616; Appx1015-1016; Appx609-610; Appx869-873.
- Meril's presubmission to the FDA was entirely voluntary and for guidance only, was not required for FDA approval, and did not even begin the FDA approval process. Appx1015-1019. Even assuming Meril's FDA presubmission was *bona fide*, it was still years from requiring clinical investigators in the United States. *See* Appx676-677, 691-692.

This evidence thus supports the conclusions that Meril imported the devices for reasons unrelated to the Landmark Trial, and that the Landmark Trial was not reasonably related to seeking FDA approval.

The district court also erred by improperly relying on self-serving declarations of Meril employees who lacked personal knowledge of the facts declared, and which are contradicted by the contemporaneous evidence. In ruling that Meril's importation of the Myval Devices "was related to the submission of information to the FDA" the district court relied entirely on the Declaration of Nilay Lad. Appx10 (citing only Appx372-374 (Lad Decl. ¶¶ 13-15, 17)). But Mr. Lad's job responsibilities had nothing to do with FDA or other regulatory submissions, recruiting clinical investigators, selling Myval Devices, or

transporting devices to trade shows. And Meril made the decision to import Myval Devices for "hands-on demonstrations" at TCT long before Lad claimed the importation decision was made. *Compare* Appx881-882, Appx884-886 (invitations for "hands-on demonstrations), *and* Appx890-893, *with* Appx602-603. Nevertheless, the district court credited Mr. Lad's testimony that Meril imported the Myval Devices to recruit clinical investigators for a so-called "FDA clinical trial," despite the contrary evidence that the importation had nothing to do with clinical trials, and that the only clinical trial planned by Meril had nothing to do with the FDA. Appx10 n.4.

Finally, although the district court purported to apply an objective standard to determine whether Meril's importation was solely for uses reasonably related to FDA submissions, it erroneously relied on Meril's representations concerning its alleged purpose for the importation. The district court held that Meril's intent for the importation was irrelevant, and thus purported to rely only on Meril's actual use of the Myval Devices. Appx 15. But lacking evidence of any actual use after importation, the district court purported to consider only the importation itself. The district court reasoned that "transporting a device to a medical conference is a necessary and predicate act for displaying the device" to recruit clinical investigators. Appx9. But the district court failed to recognize that importation is not inherently within (or outside) the safe harbor, and because Meril never actually used the Myval Devices at TCT, the only evidence connecting the importation to

recruiting investigators was Lad's declaration as to Meril's intent. Thus, the district court necessarily relied on the very intent evidence it deemed irrelevant.

The district court's several errors individually and collectively warrant reversal of its summary judgment Order and remand to allow a jury to resolve the genuine issues raised by the evidence.

ARGUMENT

I. STANDARD OF REVIEW AND MERIL'S BURDEN OF PROOF

The Federal Circuit reviews a grant of summary judgment *de novo*. *Ethicon Endo-Surgery, Inc. v. US Surgical Corp*., 149 F. 3d 1309. 1315 (Fed. Cir. 1998). Summary judgment is appropriate only when there is no genuine issue as to any material fact and the moving party is entitled to judgment as a matter of law. *Id*., citing Fed. R. Civ. P. 56(c). "In determining whether there is a genuine issue of material fact, the evidence must be viewed in the light most favorable to the party opposing the motion, with doubts resolved in favor of the opponent." *Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc.*, 145 F.3d 1303, 1307 (Fed. Cir. 1998). Thus, at the summary judgment stage, the non-movant's version of any disputed issue of fact is presumed correct. *Eastman Kodak Co. v. Image Tech. Servs., Inc.*, 504 U.S. 451, 456 (1992); *see also Union Pac. Corp. v. United States*, 5 F.3d 523, 525 (Fed. Cir. 1993) (in an appeal from a grant of summary judgment, all facts are construed in favor of non-movant). Thus, the district court is not permitted to weigh the evidence or make credibility determinations. *Tolan v. Cotton*, 572 U.S. 650, 656 (2014).

II. THE SECTION 271(e)(1) SAFE HARBOR DEFENSE

Section 271(e)(1) creates a limited safe harbor defense to a patent infringement claim, providing that "[i]t shall not be an act of infringement to . . . import into the United States a patented invention . . . solely for uses reasonably

related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs . . ." 35 U.S.C. § 271(e)(1) (emphasis added). The safe harbor defense applies to medical devices as well as drugs. *Eli Lily & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669-74, 679 (1990). The safe harbor is an affirmative defense on which the accused infringer carries the burden of proof. *Ventrassist Pty Ltd. v. Heartware, Inc.* 377 F. Supp. 2d 1278, 1286 (S.D. Fla. 2005); see *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1272 (N.D. Cal. 1991).

The existence of some FDA-related activity at or near the time of the infringement is insufficient to sweep every act of infringement into the safe harbor. *Amgen I*, 565 F. 3d at 853. Rather, Meril has to prove that "each accused activity, was for uses reasonably related to submitting information to the FDA." *Amgen II*, 944 F.3d at 1339. The Supreme Court in *Merck* confirmed that "[e]ach of the accused activities must be evaluated separately to determine whether the exemption applies." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 200 (2005).

Consequently, in *Amgen I*, this Court reversed the ITC's grant of summary judgment under the safe harbor, which was based on a blanket assumption that all activities conducted pending regulatory approval were exempt. 565 F.3d at 852. This Court noted:

> To the extent that the Commission held all importation and all uses exempt while FDA approval was pending, the safe harbor statute does not so provide. The factual questions of the purposes of the post-BLA and other challenged activities were improperly summarily decided adversely to Amgen. On remand the Commission shall consider the exempt status of each study for which question has reasonably been raised.

Id. at 853.

The safe harbor defense is highly fact-dependent. *See Integra Lifesciences I, Ltd. v. Merck KGaA*, 496 F.3d 1334, 1347 (Fed. Cir. 2007) ("The variety of experimental activity that may apply to any specific biologic or physiologic investigation reinforces the fact-dependency of the inquiry."); *Amgen II*, 944 F.3d at 1339-41 (upholding jury verdict that some acts of manufacturing were within the safe harbor and others infringing). Of course, such fact-intensive inquiries are not well suited to determination on summary judgment. For example, in *Isis Pharm., Inc. v. Santaris Pharma A/S Corp.*, No. 11-cv-2214, 2014 WL 794811 (S.D. Cal. Feb. 27, 2014), the court concluded that there was a triable issue of fact as to whether it was "objectively reasonable" for an alleged infringer to "believe that there was a decent prospect that the accused [infringing] activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." *Id.* at *13, quoting *Merck*, 545 U.S. at 200-01. The court found that the defendant was not entitled to a judgment of non-infringement as a matter of law because the determination of what was

"reasonable" involved questions of fact. *Id.* And in *Chang v. Biosuccess Biotech Co.*, 76 F. Supp. 3d 1022 (C.D. Cal. 2014), the patent holder presented evidence that the accused infringer infringed by importing the accused pharmaceutical compound for reasons unrelated to seeking FDA approval, including adding indications for use and to generate information to support foreign patent applications. *Id.* at 1036-37. Like here, the patent owner submitted evidence of the infringer's public presentations regarding the domestic uses of the imported pharmaceutical product. *Id.* at 1037. The court found that, in view of this evidence, "the present record shows that there is a triable issue of fact" as to whether the importations were reasonably related to generating data for FDA submissions. *Id.*[4]

Here too, the record shows that there are triable issues of fact which, coupled with reasonable inferences in favor of the non-movant Edwards, preclude summary judgment.

[4] See also *Scripps Clinic & Research Found. v. Genentech, Inc.*, 666 F. Supp. 1379, 1396-97 (N.D. Cal. 1987) (denying summary judgment based on evidence that sales and uses were not "solely for" meeting FDA requirements), *aff'd in part, rev'd in part*, 927 F.2d 1565 (Fed. Cir. 1991), *overruled on other grounds, Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009).

III. THE DISTRICT COURT ERRED IN GRANTING SUMMARY JUDGMENT IN FAVOR OF MERIL UNDER SECTION 271(e)(1)

A. THE DISTRICT COURT ERRONEOUSLY DISREGARDED CONTEMPORANEOUS EVIDENCE AND FAILED TO VIEW THE EVIDENCE IN THE LIGHT MOST FAVORABLE TO EDWARDS

The district court erroneously held that Meril's importation of Myval Devices to the TCT Conference was protected under the safe harbor statute "because Meril is a sponsor 'responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing.'" Appx15. The Court simply accepted Meril's representation that it imported the Myval Devices to recruit clinical investigators at TCT, as alluded to in Meril's declarations. However, "at summary judgment, the judge must view the evidence in the light most favorable to the nonmoving party: if direct evidence produced by the moving party conflicts with direct evidence produced by the nonmoving party, the judge must assume the truth of the evidence set forth by the nonmoving party with respect to that fact." *T.W. Elec. Serv., Inc. v. Pac. Elec. Contractors Ass'n,* 809 F.2d 626, 630-31 (9th Cir.1987); *see also Eastman Kodak*, 504 U.S. at 456 (at summary judgment, the non-movant's version of any disputed issue of fact is presumed correct); *Tolan*, 572 U.S. at 657-60 (vacating summary judgment where court improperly weighed evidence, failed to credit non-movant's contradictory evidence, and resolved disputed issues in favor of the moving party).

Here, there is strong contemporaneous evidence from the time of the importation from which a jury could reasonably conclude that Myval Devices were imported exclusively for use as commercial sales tools. For instance, Meril's marketing personnel drafted the two marketing pieces widely distributed by Meril before TCT inviting TCT participants to experience the Myval Devices "hands-on" at TCT. Appx616; Appx884-886; Appx670; Appx890-893; Appx746-748. Meril's marketing personnel drafted the first marketing piece planning the use of imported Myval Devices before Meril ever even communicated with the FDA about Myval. *Compare* Appx884-886, *with* Appx1015-1019. And notably, neither of these invitations to experience the Myval Devices at TCT mentioned clinical studies or Meril's purported desire to recruit clinical investigators. Appx884-886; Appx890-892; Appx746-748.

Significantly, the evidence most directly related to the imported Myval Devices instructed Meril's sales personnel on how to sell the valves at TCT: "Do not make any sales or offers for sale at the conference, or while in the United States or the US market. **You can make offer for other countries**." Appx907-909 ("Instructions for TCT 2019 for Mval THV System)" (emphasis added). The same document instructs them: "Do not carry too many demo units" (*id.*), thus linking the imported Myval Devices to commercial sales activity.[5] Ignoring this evidence,

[5] The Instructions for Myval also stated: "If possible, refer discussions of pricing, delivery, and other commercial topics to representatives outside the US for

the district court found "transportation of the Myval Samples to the TCT Conference (**with no sales or offers for sale**) was an exempt act." Appx15 (emphasis added). The district court's finding that "no sales or offers for sale" occurred at TCT is clearly rebutted by Meril's Instructions to its TCT marketing team to "make offer for other countries." This finding alone, in view of the contrary evidence that the district court was required to accept, warrants reversal.

Significantly, Meril's "Instructions for TCT 2019 for Myval THV System," like its TCT invitation and email blast, never mention the FDA or the recruitment of clinical investigators. Appx907-909. Meril admitted that it planned and held only one meeting with prospective clinical investigators at TCT, yet Meril did not bring the imported Myval Devices to that meeting, and never even planned to. Appx618; *see* Appx705. In fact, Meril never showed the Myval Devices to a single clinical investigator at TCT. Appx373-374. Thus, the importation of the Myval Devices did not facilitate, and was not in any way related to, any recruitment activities of Meril.

The evidence also reveals that Meril's *marketing* personnel brought a simulator to demonstrate Myval Devices at TCT. Appx617, 625. However, Sanjeev Bhatt, Meril's principal recruiter for clinical trials, testified that he rarely uses sample devices and never used a simulator to recruit investigators. Appx669.

---

the US market." Appx909. Thus, not only did Meril instruct its sales personnel that they could make offers for other countries, they could even discuss U.S. sales, while referring the detailed terms to representatives outside the U.S. *Id.*

Nor did Meril's head of clinical research, Dr. Ashok Thakar, use sample devices, at medical conferences or otherwise. Appx705. Instead, Mr. Bhatt used PowerPoint presentations as his primary recruiting tool. Appx669.

From this evidence, a jury could reasonably conclude that Meril imported the Myval Devices solely to support commercial sales, rather than to recruit clinical investigators. The contemporaneous evidence directly contradicts the Meril declarations upon which the district court relied. Mr. Lad at best *implied* that Meril imported its devices to recruit clinical investigators, but he never expressly said so. He stated that TCT "provided a valuable opportunity for Meril to expand its network and identify potential clinical researchers for the FDA clinical trials . . .." Appx372. He testified that he flew the devices to San Francisco for TCT, but never connected that importation with "identifying potential clinical researchers." *Id*. The closest he came was stating, "Meril *considered* showing the Myval System to potential clinical investigators at the TCT conference," but decided not to do so because of technical difficulties with a simulator. Appx374 (emphasis added). And even the purported technical difficulties with the simulator are unsupported by contemporaneous evidence. Thus, Meril's declarations stopped shy of saying that the importation was indeed for use in recruiting clinical investigators. Yet the district court made that leap, and did so despite the contrary evidence discussed above.

Meril's argument that it was recruiting clinical investigators for its "Landmark Trial" raises further material issues of fact for a jury to decide. This Court and others have recognized that certain clinical studies are not protected, including post-approval studies "conducted for marketing purposes, with the objective of trying to distinguish" the device at issue from a competitive product. *Amgen I*, 565 F.3d at 852-53. Further, otherwise infringing acts undertaken in connection with foreign clinical investigations are not within the statute. *NeoRx*, 877 F. Supp.at 208-209 (denying summary judgment in part because "the lack of a clear indication that [foreign clinical] work was submitted, or to be submitted, to the FDA argues in favor of a determination that his studies were not reasonably related to FDA submission").

Here, the evidence shows that Meril's Landmark Trial was and is a commercially motivated comparative study to be conducted exclusively outside the United States. *See* Appx912; Appx915-916; Appx926, 946-958. All contemporaneous documents up to the time of Meril's importation show that the Landmark Trial was wholly unrelated to any FDA approval. The evidence contradicts Meril's implication that its importation was related to plans to conduct "clinical studies in the United States." Appx372-374. At least seven contemporaneous documents state that, around the time of the importation and during TCT, Meril had no plans for domestic investigation sites for the Landmark

Trial. Appx590 (citing Appx842; Appx912; Appx915-916; Appx926, 946-958; Appx1013; Appx1015-1016; Appx1021-1022).

From this evidence, a jury could reasonably conclude that the Landmark Trial is entirely unrelated to generating clinical data for FDA submissions. Indeed, this Court has recognized that clinical trials are sometimes performed for purposes that are not protected under the safe harbor, such as a marketing study to distinguish a product from its competitors. *Amgen I*, 565 F.3d at 852-53 (denying summary determination of safe harbor defense and requiring factual inquiry into purpose of clinical studies); *see also Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1070 (Fed. Cir. 2011) (safe harbor does not apply to the studies that were not *mandated* by the FDA and were not for the purpose of "expedit[ing] development of information for regulatory approval"); *Amgen II*, 944 F.3d at 1340 (sustaining jury verdict rejecting defense where expert had "testified that [the accused infringer] was not **required** to manufacture additional batches after it made its 2012 batches" for FDA approval) (emphasis added).

Where the evidence permits a jury to conclude that the alleged infringing conduct is solely for commercial uses, the infringing conduct does not fall within the safe harbor. For instance, in *Amgen II*, Amgen sued Hospira for infringing Amgen's patented process for making a drug substance. *Id.* at 1332-33. Hospira manufactured twenty-one batches of the substance, and the jury found that the manufacturing of seven batches was protected under the safe harbor, while the

manufacturing of the other fourteen was not. Two of the protected batches were used for qualifying Hospira's manufacturing process and some alternate equipment, and five were used for a mandatory pre-approval inspection by the FDA. *Id.* at 1339. The jury found that all other batches were not exempted by the safe harbor in part because evidence showed they were manufactured to build commercial inventory. Hospira argued that its commercial intent was irrelevant, but the court disagreed, stating that, while Hospira's "decision to manufacture its . . . 'commercial inventory' was not dispositive of the Safe Harbor defense, . . . this evidence was probative of whether Hospira's use of Amgen's patented process was reasonably related to seeking FDA approval." *Id.* at 1340.

In granting summary judgment here, the district court dismissed the extensive evidence that Meril imported the Myval Devices for commercial uses. Rather, it erroneously found, based exclusively on Meril's litigation declarations, that the importation "was reasonably related to the submission of information to the FDA." Appx10. The district court appeared to reason based on this Court's *Abtox* decision that, once an otherwise infringing act is determined to be reasonably related to obtaining FDA approval, Meril's intent or alternative uses for the importation were irrelevant. Appx14-16, 16 n.7 (citing *Abtox, Inc. v. Exitron Corp.* 122 F.3d 1019, 1330 (Fed. Cir. 1997)). But in making the initial determination that the importation was reasonably related to obtaining FDA approval, the district court failed to draw all reasonable inferences in favor of

Edwards, the non-moving party. Indeed, the district court failed even to consider that evidence because it relegated it to "alternative uses," when, in fact, all the contemporaneous evidence supports that selling the Myval Devices was the only use for which Meril imported them. Moreover, the district court ignored the evidence of Meril's commercial intent, even though this Court had determined that such evidence is at least "probative of whether [the alleged infringement] was reasonably related to seeking FDA approval." *Amgen II*, 944 F.3d at 1340.

The district court thus failed to properly acknowledge key evidence offered by Edwards, and hence "the court below neglected to adhere to the fundamental principle that at the summary judgment stage, reasonable inferences should be drawn in favor of the nonmoving party." *Tolan*, 572 U.S. at 660.

B. THE DISTRICT COURT RELIED INSTEAD ON DECLARATIONS FROM MERIL EMPLOYEES WHO LACKED PERSONAL KNOWLEDGE

In considering Meril's motion for summary judgment, the district court was required to view any inferences reasonably drawn from the evidence in the light most favorable to Edwards. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587-88 (1986). It failed to do so, and instead, it appears the Court principally relied on self-serving declarations from Meril employees who often lacked personal knowledge of the facts declared. Specifically, the district court erred by crediting Meril's uncorroborated declaration testimony as the sole basis for finding that Meril's importation "was reasonably related to the submission of

information to the FDA," and thus, "Meril's transportation of non-commercial Myval Samples to the TCT Conference is exempt under the safe harbor." Appx10 (citing **only** Appx372-374 (Lad Decl. ¶¶ 13-15, 17)).

As a threshold matter, the district court's binary statement that the Myval Samples were "non-commercial," apparently based on the fact that Myval Devices were not approved for sale in the United States, ignores the undisputed evidence that they were approved for sale in Europe, and that the TCT Conference was a huge international marketing opportunity. *See supra* Statement of Facts §§ I-II. The district court also appeared to overlook at least the following bases for a reasonable inference that Meril's importation was to support its sales efforts entirely unrelated to any clinical recruiting or FDA-related activities:

(1) the fact that Meril's marketing personnel drafted Meril's promotional materials for TCT, inviting physicians to experience the Myval Devices "hands-on" at TCT, and the absence of any reference to clinical recruitment in these materials, even though similar invitations for other trade shows specifically mention Landmark Trial investigator meetings (*compare* Appx616, Appx884-886, Appx670, Appx890-892, *and* Appx746-748, *with* Appx964-965 (e-blast sent to London Valves conference attendees advertising "9 Landmark Trial investigator meetings"));

(2) the explicit permission to "make offer for other countries" and the absence of any reference to recruiting clinical investigators for FDA submissions

in the contemporaneous Instructions to all Meril employees attending TCT (Appx907-909);

(3) the evidence that Meril never even planned to bring the imported Myval Devices to its only meeting with potential clinical investigators at TCT (Appx618; *see* Appx705);

(4) Meril's principal clinical recruiter's testimony that he used PowerPoint presentations rather than actual demonstration valves to recruit investigators (Appx669);

(5) the fact that Meril never used or demonstrated the imported devices at TCT at all (Appx373-374);

(6) the fact that the imported devices were physically transported by Meril's employee Nilay Lad, whose job functions are entirely unrelated to clinical trials or clinical recruiting (Appx370, 372-374; Appx612-613);

(7) the fact that the Landmark Trial was a post-EU-approval trial to establish market credibility against competing devices, rather than a single-arm trial typical for regulatory approval (Appx370; Appx588-589; Appx912; Appx591; Appx915; Appx923, 946, 953; Appx969, 996-997; Appx657);

(8) the fact that Meril's only contemporaneous written references to the Landmark Trial did not involve any U.S. sites that Meril knew would be required for FDA submissions (Appx1021-1022; Appx1015-1016; Appx946, 953; Appx677; Appx716);

(9) the fact that Meril first contacted the FDA *after* it had already decided to import its Devices to TCT, *after* the same devices had been seized for alleged patent infringement at a prior trade show in France, and *after* Meril consulted with its attorneys about its plan to import the devices to TCT (Appx884-886; Appx616; Appx1015-1019; Appx547; Appx609-613; Appx869-873); and

(10) the fact that Meril routinely ignored its own FDA consultant and FDA guidance regarding the voluntary presubmission and study design, signaling it had no genuine plans to convert the Landmark Trial to one that could be used for FDA approval (Appx1036; Appx1047; Appx1049-1050).[6]

All of the foregoing support the inevitable conclusion that factual issues abound as to two major factual issues. First, whether Meril imported the Myval Devices to recruit clinical investigators, given the extensive contemporaneous evidence that it planned to use the imported Myval Devices solely as commercial sales tools. In contrast, no documentary evidence connected the imported Myval Devices to "recruiting clinical investigators." Second, there was a triable issue of fact as to whether it was "objectively reasonable" for Meril to "believe that there was a decent prospect that the [importation] would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the

[6] In all public presentations about the Landmark Trial, both before and after importing Myval Devices for TCT, Meril presented it as an entirely OUS trial. Appx588-589; Appx910, Appx912; Appx923, Appx946, Appx953; Appx969, Appx996-997; *see* https://clinicaltrials.gov/ct2/show/NCT04275726?term=myval&draw=2&rank=2.

processes by which the FDA would decide whether to approve the product in question." *Isis Pharm.*, 2014 WL 794811 at *13 (quoting *Merck*, 545 U.S. at 200-01) (emphasis added).

Here, the evidence supports a finding that it was not objectively reasonable for Meril to believe that importing devices, allegedly to recruit clinical investigators for a post-EU-approval OUS trial, would contribute "relatively directly" to generating relevant information for the FDA to approve the Myval Devices. Indeed, Meril knew that the FDA would require a trial with mostly U.S. subjects and did not believe that sample devices were useful recruiting tools in any event. The district court also failed to consider the preliminary and voluntary nature of Meril's FDA presubmissions. *See* Appx9. Moreover, to the extent the district court held that Meril believed that importing the Myval Devices would contribute relatively directly to FDA approval and that its belief was "objectively reasonable," it did so solely based on the declaration of Mr. Lad. But Mr. Lad had no experience in that area, and his declaration was completely lacking in establishing a foundation for his purported knowledge. Appx612-613; Appx370.

It is well-settled that a court should not grant summary judgment based solely on an uncorroborated, self-serving declaration (particularly in light of contradicting contemporary evidence), just as it cannot deny summary judgment based solely on an uncorroborated, self-serving declaration. *Villiarimo v. Aloha Island Air, Inc.*, 281 F.3d 1054, 1059 n.5, 1061 (9th Cir. 2002) (holding that the

district court properly disregarded a declaration that included facts beyond the declarant's personal knowledge and did not indicate how she knew the facts to be true) (*citing Kennedy v. Applause, Inc.*, 90 F.3d 1477, 1481 (9th Cir. 1996)); *Hopkins v. Andaya*, 958 F.2d 881, 888 (9th Cir. 1992) (a single contemporaneous medical record was sufficient to overturn summary judgment in favor of defendant, which the district court granted based on the defendant's self-serving and uncorroborated deposition testimony).

Lad's declaration, insofar as it purports to support a safe harbor defense, also concerns matters on which he clearly lacks personal knowledge. His job responsibilities in August and September of 2019 had nothing to do with regulatory submissions, recruiting clinical investigators, selling Myval Devices, or transporting devices to trade shows. Appx612-614. Lad lacks any experience related to FDA submissions or clinical trials, and his only role with respect to the Myval Devices was managing litigation. *Id.* Yet his declaration purports to explain the FDA approval process for heart valves and its requirements with respect to OUS and domestic clinical trials. Appx370-373. And the district court accepted that explanation despite contrary evidence that the Landmark Trial was unrelated to FDA submissions. *See* Appx9.

Further, Lad was not involved in Meril's announcements concerning its intention to bring Myval Devices to TCT for hands-on demonstrations. Appx616,

619-620.[7] Indeed, Lad's only involvement with Myval was managing litigation. Appx612-613.

Accordingly, the district court erroneously credited the Lad Declaration, failed to acknowledge the contradicting contemporaneous evidence, and neglected to draw reasonable inferences from that evidence in favor of Edwards. These errors warrant reversal of the district court's grant of summary judgment.

C. THE DISTRICT COURT PURPORTED TO APPLY AN OBJECTIVE STANDARD YET RELIED ON MERIL'S ALLEGED SUBJECTIVE INTENT FOR THE IMPORTATION

The district court purported to apply an objective standard to determine whether Meril's importation was solely for uses reasonably related to FDA submissions, noting that "consistent with the language of the statute, the safe harbor inquiry focuses on acts or uses, and not on purposes, intent or motive." Appx7. As acknowledged by the district court, the safe harbor statute delineates several potentially infringing acts – i.e., making, using, offering to sell, selling, or importing – that might fall within the safe harbor if certain conditions are met. Appx8. However, in describing those conditions the statute separately refers to "uses" of the accused devices. 35 U.S.C. § 271(e)(1) ("It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import

[7] Lad testified that he and Mr. Bhatt did not decide to import Myval Devices until a few days before TCT, but Meril's TCT invitations and email blast show that the decision was made much earlier. Appx602-603; Appx882; Appx884-886; Appx890-893. This is yet another factual dispute that the district court overlooked.

into the United States a patented invention . . . solely for **uses** reasonably related to the development and submission of information under Federal law . . .") (emphasis added). This distinction is significant because the infringing acts, such as importation or manufacture, are not inherently related, nor unrelated, to submitting information to the FDA. *See, e.g.*, *Amgen II*, 944 F.3d at 1340 (finding some manufacturing activities protected and others infringing); *Chang*, 76 F. Supp. 3d at 1035 (holding that defendant had "not presented evidence sufficient to establish that this importation of TPA was for the sole purpose of developing information to submit to the FDA"). However, the dichotomy in the statutory language has led one district court to stress that "the availability of the exemption turns on actual uses." *Intermedics*, 775 F. Supp. at 1275. "[Courts are] to focus on conduct ('uses') that actually has occurred (as opposed to uses to which a party might put its product in the future)." *Id.* at 1278 (emphasis added). "[W]e simply ask: are these actual uses 'solely . . . reasonably related to the development and submission of information' to the FDA." *Id.* at 1280. This Court has also held that "[t]he statute . . . does not look to the underlying purposes or attendant consequences of the activity . . . as long as the **use** is reasonably related to FDA approval." *Abtox*, 122 F.3d at 1030 (emphasis added).

Here, the district court appeared to overlook the statute's distinction between the potentially infringing conduct (make, use, offer to sell, sell, import), on the one hand, and the uses that may bring that conduct within the safe harbor (uses

reasonably related to an FDA submission), on the other hand. It concluded that "importation by itself (without actual use) can fall within the safe harbor." Appx8. The district court quoted *Abtox* in further holding that "'[Meril's] intent or alternative uses are irrelevant to its qualification to invoke the section 271(e)(1) shield.'" *Abtox*, 122 F.3d at 1030. Accordingly, Defendants' underlying purposes are not relevant to the safe harbor inquiry." Appx15. This holding misreads *Abtox* and ignores *Amgen II*, which confirmed that evidence of commercial intent is at least probative of whether use of the patented process was reasonably related to seeking FDA approval. 944 F.3d at 1340. Indeed, because there was no actual post-importation use, evidence of Meril's intent appears to be the **only** probative evidence on applicability of the safe harbor.

The district court ignored the critical part of this Court's holding, namely that "**As long as the activity is reasonably related to obtaining FDA approval**, [the accused infringer's] intent or alternative uses are irrelevant to its qualification to invoke the section 271(e)(1) shield." *See* Appx15 (quoting only a portion of *Abtox*, 122 F.3d at 1030 (emphasis added)). Thus, before Meril's intent and alternative uses can be deemed irrelevant, a determination must be made that "the activity is reasonably related to obtaining FDA approval." Given there was no actual use after importation, the only activity to be examined is the importation itself, and the only evidence connecting the importation to obtaining FDA approval is evidence of Meril's subjective intent. However, that evidence (principally

Meril's self-serving declarations) is disputed by other evidence of Meril's solely commercial intent. The district court thus erred in deeming Meril's intent irrelevant in the absence of evidence of a protected use.

Regardless of whether the safe harbor statute requires an actual use in addition to the infringing act, the district court erred in granting summary judgment. To the extent an actual use is required, there was no actual use beyond mere importation. To the extent no actual use is required, the only evidence that connects Meril's importation to a use that falls within the safe harbor is the disputed evidence of Meril's subjective intent. That extensive evidence creates genuine issues of fact, particularly when all reasonable inferences are drawn in favor of Edwards.

It is undisputed that Meril never actually used the imported Myval Devices at TCT. Appx373-374; Appx618. Meril never showed them to anyone and never removed them from the bag used to transport them. *Id*. Accordingly, to the extent the safe harbor statute requires an "actual use," there was none. Indeed, if the statute requires actual use, and intent is irrelevant, the district court erred because it relied solely on evidence of Meril's alleged intent to use the Myval Devices to recruit investigators. And again, importation itself cannot be inherently exempt under the safe harbor because some "generic" acts of infringement (manufacturing, importation, etc.) are covered, and some are not. *Amgen II*, 944 F.3d at 1340 (manufacturing); *Chang*, 76 F. Supp. 3d at 1036 (importation).

On the other hand, if Meril's intended use for the imported devices is relevant (including because there was no actual use), a wealth of contemporaneous evidence contradicts any implied finding by the district court that Meril intended to import the Myval Devices for recruiting clinical investigators to develop FDA-related data. A fact-finder considering that evidence could reasonably conclude that Meril's purpose in importing its valves to TCT was solely commercial in nature. Again, it was Meril's marketing personnel, not its clinical personnel, who invited TCT attendees to experience "hands-on" Myval sessions at TCT. Appx882; Appx884-886; Appx890-893; Appx616, 619-620; Appx670. These invitations never mentioned clinical investigators or clinical trials. Appx882; Appx884-886; Appx890-893. Meril admitted it never even planned to bring its devices to its only meeting with potential clinical investigators at TCT. Appx618. And its principal recruiter for clinical trials testified that he uses PowerPoint presentations rather than sample devices for recruiting purposes. Appx669. Thus, the evidence at least supports, if not requires, the inference that Meril's purpose for importing the Myval Devices to TCT was solely for use as a commercial sales tool, and not for any use reasonably related to generating information for the FDA.

Finally, the district court also erred in holding that "demonstrations at medical conferences are covered by the Section 271(e)(1) safe harbor," regardless of actual use or intended use. Appx8-9. In the cases cited by the district court, it was undisputed that at least one purpose of the accused infringer's actual use was

recruitment of clinical investigators for an FDA-sanctioned clinical trial. *See Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1522-23 (Fed. Cir. 1992) (undisputed that the defendant also demonstrated the device to clinical investigators); *see also Intermedics*, 775 F. Supp. at 1287 (patent owner did not dispute that defendant's actual demonstrations were, in part, reasonably related to obtaining FDA approval). Moreover, the defendants in both cases already had IDEs, so unlike Meril they were actually permitted to conduct clinical trials in the United States. *Telectronics*, 982 F.2d at 1521; *Intermedics*, 775 F. Supp. at 1276.

Here, by contrast: (a) there was no actual demonstration of the Myval Devices to clinical investigators, or any other use, (b) Meril was and still is nowhere near obtaining the IDE approval required for domestic clinical trials, and (c) it is very much disputed based on the contemporaneous evidence that recruiting clinical investigators for FDA approval was Meril's purpose for importing its devices. Moreover, the evidence supports an inference that Meril's sole purpose for importing Myval Devices was to support its commercial sales efforts, and the importation was wholly unrelated to recruiting clinical investigators and wholly unrelated to any FDA submission.

In sum, the district court erred in granting safe harbor protection on summary judgment to Meril's infringing act of importing the Myval Devices. The district court acknowledged that Meril did not use the Myval Devices once imported, yet erroneously found that Meril's actual use reasonably related to FDA

submissions. In doing so, it erroneously relied on Meril's declarants' stated intent for the importation—the recruitment of clinical investigators for a non-existent FDA trial. But Meril's own documents and admissions would permit a reasonable fact-finder to conclude that Meril imported the Myval Devices for its marketing employees to use as commercial sales tools at TCT. Thus, the grant of summary judgment cannot stand.

CONCLUSION AND RELIEF SOUGHT

Edwards respectfully submits that the Court should reverse the Judgment and the district court's Order granting summary judgment, and direct the district court that Meril's safe harbor defense should be decided at trial, if trial of Edwards' patent infringement claims is otherwise appropriate.

DATED: November 7, 2022 By: */s/ Christy G. Lea*
Christy G. Lea

Steven M. Hanle, *Principal Attorney*
STRADLING YOCCA CARLSON & RAUTH PC

Christy G. Lea
KNOBBE, MARTENS, OLSON & BEAR, LLP

Carlo Van den Bosch
Gazal Pour-Moezzi
SHEPPARD MULLIN RICHTER & HAMPTON LLP

Attorneys for Plaintiffs-Appellants
Edwards Lifesciences Corporation and
Edwards Lifesciences LLC

INDEX TO APPENDED MATERIALS

ADDENDUM

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

EDWARDS LIFESCIENCES CORPORATION, et al.,

Plaintiffs,

v.

MERIL LIFE SCIENCES PVT. LTD., et al.,

Defendants.

Case No. 19-cv-06593-HSG

ORDER GRANTING MOTION FOR SUMMARY JUDGMENT AND GRANTING IN PART AND DENYING IN PART MOTIONS TO SEAL

Re: Dkt. No. 67

Pending before the Court is Defendants Meril Life Sciences PVT. LTD ("Meril Life Sciences") and Meril, Inc. (collectively, "Defendants," or "Meril") Motion for Summary Judgment, for which briefing is complete. Dkt. Nos. 67 ("Mot."), 82 ("Opp."), and 90 ("Reply"). The parties have also filed administrative motions to seal ("Motions to Seal") portions of their briefs and exhibits related to the Motion. *See* Dkt. Nos. 66, 81, 87, 89. On September 24, 2020, the Court held a hearing on the Motion. Dkt. No. 96. For the reasons below, the Court **GRANTS** Defendants' Motion for Summary Judgment, and **GRANTS IN PART** and **DENIES IN PART** the Motions to Seal.

I. BACKGROUND[1]

Meril Life Sciences is an India-based, global medical device company that was founded in 2007. Declaration of Nilay Lad (Dkt. No. 67-3, "Lad Decl.") ¶ 2. Meril, Inc. is a wholly owned subsidiary of Meril Life Sciences. *Id.* Meril created a "Myval" branded transcatheter heart valve, which is designed to be used with a "Navigator" delivery system (collectively, the "Myval System"). *Id.* ¶ 3; Declaration of Sanjeev Bhatt (Dkt. No. 67-1, "Bhatt Decl.") ¶ 3. Edwards

[1] The following facts are undisputed unless otherwise noted.

Lifesciences Corporation ("Plaintiff" or "Edwards") is a supplier of medical devices for the treatment of heart disease, including artificial heart valves. Among its best-known products are its "SAPIEN®" transcatheter prosthetic heart valves.

The Myval System is intended to treat severe symptomatic native aortic valve stenosis, a condition where the aortic valve narrows and restricts normal blood flow. *Id.* In 2016, Meril's experimentation with the Myval System led up to a cadaver procedure "to determine the feasibility of implanting the Myval transcatheter heart valve into human subjects" at the University of Washington ("UW") in January 2017. Bhatt Decl. ¶ 4. In January 2017, Meril shipped six samples of the Myval System to UW to conduct these pre-clinical investigations on cadavers, and to determine whether the Myval transcatheter heart valve could be safely implanted in future clinical studies. *Id.* Members of the UW team successfully implanted the Myval transcatheter heart valve in cadavers, which enabled Meril to plan its clinical studies with human subjects. *Id.*[2]

Meril first began conducting clinical trials for its Myval System in India in June 2017, and received approval from the Drug Controller General of India on October 31, 2018. Lad Decl. ¶ 4. In April 2019, the Myval System was granted the CE marking, which certifies its conformance to health and safety standards for products sold within the European Economic Area. *Id.* In the United States, the Myval System is considered a "Class III" medical device subject to strict regulatory standards. *Id.* ¶ 5; 21 U.S.C. § 360c(a)(1)(C) (classifying a Class III device as "for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health"). Therefore, Meril may not lawfully market or sell the Myval System in the United States without first receiving mandatory premarket approval from the United States Food and Drug Administration ("FDA"). Lad Decl. ¶ 5; 21 U.S.C. § 360c; 21 C.F.R. §

[2] Around this time, Meril also began planning a preclinical animal study for Myval with the CRF Skirball Center for Innovation in New York ("Skirball Study"). Dkt. No. 87-6 ("Stephens Decl.") Ex. 13 at 4:23-28. The Skirball Study was to investigate the feasibility of implanting the Myval System into humans, and whether Meril could do so safely in clinical studies. *Id.* In 2016, Meril sent three samples of the Myval transcatheter heart valve ("THV") and the Myval System for the Skirball Study, and six Myval Samples to UW. Bhatt Decl. ¶ 4; Stephens Decl. Ex. 13 at 4:23-28. The Skirball Study occurred on January 27, 2017, and the results were documented in a written report. Dkt. No. 90-1 ("Mayer Reply Decl.") Ex. 15.

812.20; 21 C.F.R. § 812.42.

To receive premarket approval from the FDA, Meril must first apply for and obtain an investigational device exemption ("IDE") from the FDA, identify clinical investigators to implant the device in human subjects, collect data from those subjects, and then submit the data to the FDA. Lad Decl. ¶ 5; Bhatt Dec. ¶ 5. IDE applications require sponsors to describe all preclinical testing and include reports of prior investigations. Dkt. No. 67-15, Declaration of Melanie Mayer ("Mayer Decl."), Ex. 4 at MERIL00000542.

The premarket approval process can be lengthy and difficult to navigate, and Meril began preparations ahead of its planned IDE application. First, Meril began preparing for a pre-submission to the FDA, which allows device manufacturers to request formal regulatory feedback on the device before officially engaging in the premarket approval process. Lad Decl. ¶¶ 6-7; Mayer Decl., Ex. 1 at MERIL00000404. The pre-submission program allows device makers like Meril to obtain guidance from the FDA about its premarket submissions, which in turn improves the quality of submissions and shortens total review times. Lad Decl. ¶ 6; Mayer Decl., Ex. 1 at MERIL00000404.

In May 2019, Meril imported a number of Myval System devices to a large conference in France called EuroPCR. Dkt. No. 84-1, Ex. A ("Lad Depo.") at 76-78. Edwards appears to have anticipated this importation, and filed a proceeding in France authorizing the seizure of the Myval Devices based on the alleged infringement of Edwards' European patents. *Id.* A brochure was seized that included an updated new slide on Meril's Global Clinical Program, with the first mention of a "Landmark Trial." *See* Stephens Decl. ¶ 82; Ex. 34. This "Landmark Trial" was to be a three-arm trial comparing the Myval System with the market leading devices in Europe, Edwards' SAPIEN valves and Medtronic's CoreValve Evolut valves. Dkt. No. 84-2, Ex. B ("Bhatt Depo.") at 50-51.

In late August 2019, Meril contacted the FDA to inquire about the Landmark Trial and the preliminary requirements for filing a pre-submission. Lad Decl. ¶ 7, Exs. A, B. In early September 2019, Meril also contacted CardioMed LLC, a medical device consulting company that provides regulatory and clinical trial consulting services, including for premarket approval

submissions, and sought its help in preparing a pre-submission filing to the FDA for the Myval System. *Id.* ¶ 8, Ex. C.

Meril then sought out potential clinical researchers at the 2019 Transcatheter Cardiovascular Therapeutics Conference in San Francisco ("TCT Conference")—an annual scientific symposium hosted by the Cardiovascular Research Foundation ("CRF") featuring the latest developments in interventional cardiovascular medicine, and attended by leading researchers and clinicians. *Id.* ¶ 10; Mayer Decl., Ex. 3. In advance of the TCT Conference, Meril provided CRF a digital flyer containing information about Meril's booth and its agenda at the conference. *Id.* ¶ 11. CRF then distributed this flyer to individuals and organizations who had subscribed to receive email updates about the TCT Conference. *Id.* It is undisputed, however, that the Myval System was never shown to anyone after it was imported into the United States. *Id.* ¶ 17; Lad Depo. at 95-96.

Nilay Lad, a Meril employee, traveled to San Francisco on September 24, 2019 to attend the TCT Conference. Lad Decl. ¶ 13. He carried with him two Myval THV's, Myval THV's with rubber leaflets, and two Navigator delivery systems (collectively, "Myval Samples") on his flight into San Francisco International Airport. *Id.* The Myval Samples were contained in a bag, and accompanied by a written declaration stating:

> This is to inform you that the demo samples carried by Mr. Nilay Lad is for the demonstration purpose only.
>
> It is consist [sic] of Demo samples of Medical devices. They have no commercial value & hence it is not used for any sales purpose. The demo samples are NON-STERILE. NOT FOR HUMAN USE. NOT FOR SALE. NOT APPROVED FOR SALE IN UNITED STATES. FOR DEMO PURPOSE ONLY AT TCT 2019, SAN FRANCISCO.

Id., Ex. F.

Meril had a booth at the TCT Conference from September 26 to September 28, and provided information on its cardiovascular systems, including the Myval System, in the form of visual displays and presentations to attending physicians. *Id.* ¶ 14, Exs. G-H. For the Myval System, Meril exhibited patient case studies, information on the Myval System and its use in a clinical trial, and information about the placement of the Myval System in patients. *Id.* Meril stated to conference attendees that the Myval System was not yet approved by the FDA, and that it

was not available for sale in the U.S. *Id*. Meril also discussed the details of the Myval System with several U.S. doctors to identify potential clinicians for its premarket approval application. *Id.* ¶ 15.

Meril considered showing the physical Myval System in conjunction with a simulation system that would provide potential clinicians with a hands-on opportunity to interact with the physical devices. However, because of alleged technical difficulties with the simulation system, Meril did not show the physical Myval samples at the TCT Conference. *Id.* ¶ 17. Meril also did not offer for sale or sell the Myval System to any non-U.S. customers at the TCT Conference. *Id.* ¶ 15. Because Meril did not exhibit the physical Myval Samples, Mr. Lad maintained the samples overnight in a bag in a storage room at the TCT Conference. The samples were never taken out of the bag or displayed to any conference attendees. *Id.*

On September 28, Mr. Lad gave the Myval Samples to another Meril employee, Sanjeev Bhatt, to take to Europe on September 30. *Id.*; Bhatt Decl. ¶ 6. For a short period of time after Meril attended the TCT Conference, Meril's LinkedIn page stated that 2,000 people visited its booth at the TCT Conference and that Meril had exhibited the Myval System at its booth. Lad Decl. ¶ 18. Meril later removed the LinkedIn post. *Id.*

II. LEGAL STANDARD

Summary judgment is proper when a "movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A fact is "material" if it "might affect the outcome of the suit under the governing law." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). And a dispute is "genuine" if there is evidence in the record sufficient for a reasonable trier of fact to decide in favor of the nonmoving party. *Id.* But in deciding if a dispute is genuine, the court must view the inferences reasonably drawn from the materials in the record in the light most favorable to the nonmoving party, *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587–88 (1986), and "may not weigh the evidence or make credibility determinations," *Freeman v. Arpaio*, 125 F.3d 732, 735 (9th Cir. 1997), *overruled on other grounds by Shakur v. Schriro*, 514 F.3d 878, 884–85 (9th Cir. 2008). If a court finds that there is no genuine dispute of material fact as to only a single claim or defense or as to

part of a claim or defense, it may enter partial summary judgment. Fed. R. Civ. P. 56(a).

III. DISCUSSION

Defendants contend that they did not infringe Plaintiff's patents because (1) Meril did not use or exhibit Myval samples during the TCT Conference, and (2) Meril's transportation of its Myval-branded transcatheter heart valve system to UW in 2017 and to the TCT Conference was reasonably related to its premarket submissions to the FDA, and is thus protected by the safe harbor exemption under 35 U.S.C. § 271(e)(1).

A. Safe Harbor Application

Congress enacted 35 U.S.C. § 271(e)(1) to address issues created by the legal requirements for pre-market FDA approval of drugs and medical devices, particularly those involving patented inventions. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669-70 (1990). One of these issues was that third parties wishing to sell the patented product upon patent expiration had to engage in a lengthy FDA approval process, essentially creating a *de facto* extension of the patent while FDA approval was pending. *Id.* at 670.

To address this problem, Congress enacted the safe harbor of Section 271(e)(1), which provides that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." Put differently, Section 271(e)(1) allows competitors, before the expiration of a patent, to engage in otherwise infringing activities if the use is "reasonably related to" obtaining regulatory approval. Courts routinely decide the applicability of the safe harbor at the summary judgment stage. *See, e.g.*, *Genentech, Inc. v. Insmed Inc.*, 436 F. Supp. 2d 1080, 1095 (N.D. Cal. 2006); *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1059 (Fed. Cir. 2011).

Section 271(e)(1) undisputedly can apply to medical devices like the Myval System. *Eli Lilly*, 496 U.S. at 661. Section 271(e)(1) "provides a wide berth for the use of patented [inventions] in activities related to the federal regulatory process." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005); *see also Med. Diagnostic Labs., L.L.C. v.*

Protagonist Therapeutics, Inc., 298 F. Supp. 3d 1241, 1247 (N.D. Cal. 2018). The Supreme Court has explained that "[Section] 271(e)(1)'s exemption from infringement extends to *all* uses of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA [Federal Food, Drug, and Cosmetic Act]," which "necessarily includes preclinical studies." *Merck KGaA*, 545 U.S. at 202 (emphasis in original). The safe harbor also applies regardless of the phase of research, and even if the information is never ultimately submitted to the FDA as part of an approval application. *Id.* at 202, 205 ("There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included."); *see also Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1027 (Fed. Cir. 1997) (finding the safe harbor applicable where, "[a]t the time of this litigation, [defendant] had neither filed an application for approval with the FDA nor otherwise marketed the device").

As the Supreme Court explained, an activity is "reasonably related" to federal regulatory activities if an accused manufacturer has a reasonable basis for believing that a device may work to achieve a particular result, and uses the device in research that, if successful, would be appropriate to include in a submission to the FDA. *Merck KGaA*, 545 U.S. at 207; *see also Intermedics, Inc. v. Ventritex, Inc*., 775 F. Supp. 1269, 1280 (N.D. Cal. 1991) ("*Intermedics I*") (proper inquiry is whether "it [would] have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute . . . to the generation of [] kinds of information … likely to be relevant in the processes by which the FDA would decide whether to approve the product").

Similarly, consistent with the language of the statute, the safe harbor inquiry focuses on acts or uses, and not on purposes, intent or motive. *See* 35 U.S.C. § 271(e)(1) (extending protection to "uses reasonably related"). The Federal Circuit has explained that "[t]he breadth of the exemption [under Section 271(e)(1)] extends even to activities the 'actual purpose' of which may be 'promot[ional]' rather than regulatory, at least where those activities are 'consistent with the collection of data necessary for filing an application with the [FDA].'" *Momenta Pharm., Inc. v. Teva Pharm. USA Inc.*, 809 F.3d 610, 619 (Fed. Cir. 2015) (citing *Abtox*, 122 F.3d at 1027).

Plaintiff contends that the safe harbor requires an "actual use." Opp. at 16. However, as noted, the safe harbor provides that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). The statute lists each of the possibly infringing acts (making, using, offering to sell, selling, and importing) separately, making clear that importation by itself (without actual use) can fall within the safe harbor. The clause "solely for uses reasonably related to the development and submission of information" to the FDA also does not require an "actual use." As the Federal Circuit has explained, the safe harbor applies "[a]s long as the [allegedly infringing] activity [*e.g.*, making, using, selling, offering for sale, and importing] is reasonably related to obtaining FDA approval." *Abtox*, 122 F. 3d at 1030.

Here, Defendants contend that there can be no genuine dispute that all the accused activities were directed at furthering Meril's clinical investigation of its Myval System for future FDA approval and thus fall squarely within the scope of the safe harbor. Plaintiff alleges two acts of infringement: (1) Meril "imported" the Myval System into the United States in 2017 so that UW could conduct a pre-clinical cadaver study (Dkt. No. 51 ¶ 40); and (2) Meril "imported" and "exhibited" at least one Myval System at the 2019 TCT Conference. *Id.* ¶ 39.

i. 2019 TCT Conference

Meril contends that the shipment of samples to the TCT Conference falls within the safe harbor because Meril did not exhibit the Myval System during the TCT Conference. Lad Dec. ¶ 17. Meril states that although it transported a number of Myval Samples to the TCT Conference planning to demonstrate the physical device to potential clinical researchers, it had technical difficulties with the simulation system, with the result that the Myval Samples remained stored away during the time they were in San Francisco and were not shown to any conference attendees. *Id.* Accordingly, Meril contends that there can be no infringement.

According to the Federal Circuit, demonstrations at medical conferences are covered by the Section 271(e)(1) safe harbor. *Intermedics, Inc. v. Ventritex Co.*, No. 92-1076, 1993 WL 87405, at *3 (Fed. Cir. Feb. 22, 1993) ("*Intermedics II*") ("Assuming that these nonsale

demonstrations at medical conferences constitute an infringing use, we have held they are an exempt use that is reasonably related to procuring FDA approval of the device."); *Chartex Intern. PLC v. M.D. Personal Products Corp.*, 5 F.3d 1505, 1993 WL 306169, at *4 (Fed. Cir. 1993) (affirming summary judgment of non-infringement because exhibition of device at trade show was either a non-infringing act under 35 U.S.C. § 271(a) or exempt under the Section 271(e)(1) safe harbor). And transporting a device to a medical conference is a necessary and predicate act for displaying the device, such that the transportation of an accused device into a country for display at a medical conference is also exempt under the safe harbor. *See Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1564 (Fed. Cir. 1996) (importing accused product into the U.S. "for use in clinical trials in support of . . . application for FDA approval" is non-infringing activity); *Merck KGAa*, 545 U.S. at 202 (the safe harbor extends to "all uses" reasonably related to the development of any information for FDA purposes).

It is undisputed that as of the time of TCT Conference, Meril had taken significant steps towards obtaining FDA approval for the Myval System, including: (1) preparing a formal clinical trial synopsis for its Landmark Trial, Mayer Reply Decl. Ex. 9;[3] (2) preparing a draft presubmission to seek FDA input on its clinical trial, Dkt. No. 84-4 ("Nair Depo.") at 33:3-24; (3) communicating with the FDA regarding Meril's proposed clinical study and its presubmission, Lad Decl. Exs. A, B; and (4) hiring an FDA consultant to help with the FDA presubmission. Lad Decl. ¶¶ 8-9; Nair Depo. at 57:10-58:15. Plaintiff does not dispute these facts, and instead contends that because Meril never actually used the devices after their importation, its safe harbor defense fails as a matter of law.

[3] The Landmark Trial appears to be a post-EU-approval study to be conducted in Europe to compare the Myval System to other leading devices in the European market. Lad Decl. ¶¶ 12, 15. Plaintiff contends that the Landmark Trial is not an "FDA clinical trial" because Meril's early documents describe it as an "outside the US" trial. Opp. at 17. However, it is undisputed that FDA approval can be supported by clinical trials that include patients both within and outside of the US. Mayer Reply Decl. Ex. 14 at 1, 4; Lad Decl. Ex. A at MERIL00000442-443. Therefore, even if the Landmark Trial was an entirely "OUS" study at the time of the TCT Conference, and even if Meril was only identifying investigators at the TCT Conference for this OUS trial, and even if it was commercially motivated in part, the Landmark Trial was reasonably related to FDA approval.

The Court finds that the undisputed evidence gives rises to no genuine dispute of fact as to whether Meril's transportation of non-commercial Myval Samples to the TCT Conference is exempt under the safe harbor. Lad Decl. ¶¶ 13-15, 17.[4] It is undisputed that Meril transported the medical device to the TCT Conference, which was attended by a large number of potential clinical trial investigators. Lad Decl. ¶ 14. It is also undisputed that Meril did not sell or offer to sell its medical device at the medical conference. *Id.* ¶ 15. Therefore, Meril's transportation of the Myval Samples to the TCT Conference, where Meril did not sell or offer to sell the device, was reasonably related to the submission of information to the FDA, including educating the investigators at the TCT about the Myval System. *See id.* ¶¶ 13, 15; *Telectronics II*, 982 F.2d at 1523 (nonsale "demonstrations constitute an exempt use reasonably related to FDA approval"); *Intermedics II*, 1993 WL 87405, at *3 (nonsale demonstrations at medical conferences are reasonably related to FDA approval and exempt under the safe harbor); *see also Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1263 (Fed. Cir. 2008) ("demonstrating an implantable defibrillator at medical conference was 'reasonably related' to FDA approval because it facilitated the selection of clinical trial investigators").

ii. University of Washington Study

Meril similarly contends that its shipment of Myval Samples to UW for preclinical investigations was protected under the safe harbor. It is undisputed that the UW preclinical study investigated whether the Myval System could be safely implanted in human subjects in future clinical studies. Bhatt Decl. ¶ 4. Plaintiff appears to agree that the UW study was performed by "an internationally respected interventional cardiologist," who successfully implanted the Myval THV in cadavers and documented the entire procedure on video. Opp. at 20; Bhatt Decl. ¶ 4;

[4] Plaintiff objects to portions of the Lad Declaration and contends that Mr. Lad lacks personal knowledge of "Meril's purpose for importing the Myval Device." Opp. at 15. However, it is undisputed that Mr. Lad personally transported the Myval Samples to the TCT Conference, and he testified that he consulted with counsel and Mr. Bhatt about bringing the Myval System to the TCT Conference. Lad Decl. ¶ 13; Lad Depo. at 34:8-34:17; 60:2-61:7. In addition, Mr. Lad and Mr. Bhatt explain that Meril brought the Myval samples to the TCT Conference to identify FDA clinical trial investigators. *See* Bhatt Depo. at 64:1-65:1, 65:21-66:10; Lad Depo. at 83:16-84:1; *see also* Bhatt Decl. ¶ 5; Stephens Decl. Ex. 13 at 6:8-11. Accordingly, Plaintiff's objections to the Lad Declaration are overruled, and Mr. Lad's declaration adequately establishes personal knowledge. *See Fraser v. Goodale*, 342 F.3d 1032, 1036 (9th Cir. 2003).

Bhatt Depo. at 40:11-20.

The Supreme Court has made clear that preclinical studies appropriate for submission to the FDA during the regulatory process are protected under the safe harbor, even if the results are never ultimately submitted. *Merck KGaA*, 545 U.S. at 202, 205 ("There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included."). Meril presents undisputed evidence that the Myval Samples were related to determining the feasibility and safety of using the Myval System to implant the Myval transcatheter valve in live human subjects, which Meril needed to confirm before it could conduct clinical trials. *Id.* at 193 (safe harbor exempts preclinical studies pertaining to device safety and efficacy in humans); *Genentech, Inc. v. Insmed Inc.*, 436 F. Supp. 2d at 1095 (applying safe harbor where third-party consultant research using the accused compound "was for FDA purposes" and where, "[w]ithout FDA approval, Defendants could not sell their drug on the market"); *Intermedics I*, 775 F. Supp. at 1285 (where safety certification by a third party was required to conduct FDA clinical tests, such testing was protected by safe harbor).

It is also undisputed that the UW clinicians used the Myval System to place a Myval THV in a cadaver. Bhatt Decl. ¶ 4. And Meril used the data collected during this investigation to understand the mechanics of positioning the Myval transcatheter valve in a human body. *Id.* There is also no dispute that, to receive premarket approval for Myval, Meril needed to first obtain an IDE from the FDA, and that the FDA requires the IDE application to include a "report of prior investigations [that] must include reports of all prior clinical, animal, and laboratory testing of the device." Lad Decl. ¶ 5; Mayer Decl. Ex. 4 at MERIL00000542; *see* Opp. at 19. Therefore, the Court finds that there is no genuine dispute that the UW preclinical study produced (and was therefore reasonably related to) the types of information that are relevant to the FDA approval process.

Plaintiff nevertheless contends that "Meril did not submit any information from this study in connection with either of its FDA pre-submissions." Opp. at 20. Meril counters that Plaintiff misunderstands the FDA process, and that Meril is only at the presubmission stage of the FDA

process, during which it is getting FDA input on certain information it plans to submit in its later IDE. Bhatt Depo. at 128:25-129:12; Mayer Reply Decl. Ex. 12. When Meril reaches the IDE stage, the FDA rules require Meril to submit the UW cadaver study video as part of its IDE. Mayer Decl. Ex. 4 at MERIL00000542. In any event, the Supreme Court has made clear that the safe harbor applies to preclinical studies even if the data is not ultimately submitted to the FDA, so Plaintiff's argument fails as a matter of law. *Merck*, 545 U.S. at 207 (safe harbor "does not become more attenuated (or less reasonable) simply because the data from that experiment are left out of the submission . . . to the FDA").

Plaintiff also contends that Meril did not describe "what information the cadaver study would generate that is relevant to an IDE or PMA." Opp. at 19. However, Meril explained that it used the data collected during the UW preclinical study to understand the mechanics of positioning the Myval THV in the human body and to determine the feasibility of safely implanting the valve in live human subjects. Bhatt Decl. ¶ 4. Plaintiff does not dispute this, and it is undisputed that the UW study data must be submitted to FDA. In the end, Plaintiff's argument is unpersuasive, and no more is required for the safe harbor to apply on this record.[5]

Lastly, leaving no potentially saving angle unexplored, Plaintiff also asserts that there were a number of additional importations as to which Defendants did not move for summary judgment. Opp. at 18-19. Defendants also appear to move for summary judgment as to the Skirball Study only in their Reply, as there is no mention of the study in the motion. Reply at 6.

However, none of these "additional" importations or acts of infringement, including the Skirball Study, are mentioned by Plaintiff in its Amended Complaint, which only addresses the UW study and the TCT Conference. *See, e.g.*, Dkt. No. 51 at ¶¶ 38-40. Although Plaintiff did include boilerplate language saying that "Plaintiffs believe that the factual contentions set forth in

[5] That Meril discussed the UW preclinical study in a Continuing Medical Education presentation in Kolkata, India two years later does not alter the applicability of the safe harbor. *See* Bhatt Dec., Ex. AA. The Federal Circuit has repeatedly explained that subsequent disclosure or use of information from preclinical or clinical studies—even for commercial purposes—does not negate application of the safe harbor. *See Classen Immunotherapies, Inc. v. Elan Pharm., Inc.*, 786 F.3d 892, 898 (Fed. Cir. 2015) ("subsequent disclosure or use of information obtained from an exempt clinical study, even for purposes other than regulatory approval, does not repeal [the safe harbor] exemption of the clinical study").

this claim for relief will likely have further evidentiary support after a reasonable opportunity for further investigation or discovery," *id.* at ¶¶ 86, 94, this is insufficient to properly plead some unspecified number of additional unnamed potential acts of infringement. Therefore, it is immaterial whether Defendant sought summary judgment as to these unasserted theories. Accordingly, while the Court declines to grant summary judgment as to these acts based on an argument first raised in Defendant's reply, the Court finds that the additional purported acts of infringement are not presently before the Court in this action. *Hauschild v. City of Richmond*, No. C 15-01156 WHA, 2016 WL 3456620 at *5 (N.D. Cal. June 14, 2016) (disregarding "Plaintiff's new theory" in a motion for summary judgment where the complaint did not put defendants on notice about the evidence it would need to defend against plaintiff's new allegations) (citing *Pickern v. Pier 1 Imports (U.S.), Inc*., 457 F.3d 963, 969 (9th Cir. 2006) (affirming grant of summary judgment in favor of defendant where "the complaint gave the Appellees no notice of the specific factual allegations presented for the first time in [plaintiff's] opposition to summary judgment.")); *see also Bell v. F.D.I.C.*, No. C09-0150RSL, 2011 WL 2011497 at *3 (W.D. Wash. May 23, 2011) ("This claim was not asserted in the Amended Complaint, however, and cannot be added to this litigation in response to a summary judgment motion."); *Gilmour v. Gates, McDonald and Co.*, 382 F.3d 1312, 1314–15 (11th Cir. 2004) ("[T]he Supreme Court has mandated a liberal pleading standard for civil complaints … This standard however does not afford plaintiffs with an opportunity to raise new claims at the summary judgment stage … At the summary judgment stage, the proper procedure for plaintiffs to assert a new claim is to amend the complaint in accordance with Fed.R.Civ.P. 15(a).").[6]

[6] In any event, Plaintiff only relies upon a customs declaration for the simulator that lists "Navigator." Reply at 14; Stephens Decl. Ex. 26. This "Navigator" refers to a modified device that is built into the simulator and that is missing the balloon portion. Mayer Reply Decl. ¶ 34. The Court fails to see the relevance of Plaintiff's argument when the referenced "Navigator" lacks an "inflatable balloon" as required by Plaintiff's patent claims. As to the Skirball Study, it is undisputed that the study was a preclinical study to investigate Myval System's performance and to inform the feasibility of future clinical trials in live human subjects. Opp. at 4; Stephens Decl. Ex. 13 at 4:8-15; Bhatt Depo. at 84:15-20. And it is clear that Defendants provided the relevant discovery surrounding the Skirball Study. Mayer Reply Decl. ¶ 31. Accordingly, it appears that the safe harbor would also apply to the Skirball Study for the same reasons the Court has found it applies to the UW study, namely that the FDA requires Meril to submit all Myval preclinical studies—including the Skirball study—with Meril's IDE.

B. Commercial Purpose

Plaintiff contends that the safe harbor also does not apply because Meril had a commercial purpose when it brought the Myval samples to the UW and to the TCT Conference. Defendants contend that Plaintiff's argument fails for two reasons: (1) Defendants' purported purpose is irrelevant to whether the accused use falls within the scope of Section 271(e)(1), and (2) even if Defendants' purpose was relevant, Meril's purpose in transporting the samples into the U.S. in 2017 and 2019 was to support future clinical trials to seek premarket approval from the FDA.

As discussed above, whether the safe harbor applies turns on the objective question of whether the actions taken with respect to a device are reasonably related to FDA approval, and the only relevant acts are those that would otherwise constitute patent infringement under Section 271. *Eli Lilly*, 496 U.S. at 663 (inquiry is whether the safe harbor "renders activities that would otherwise constitute patent infringement noninfringing"). If Defendants' otherwise infringing act is reasonably related to FDA approval, the safe harbor applies regardless of the purported purpose behind the use. *Momenta Pharm.*, 809 F.3d at 619.

In *Abtox*, the Federal Circuit affirmed the grant of summary judgment of non-infringement, even though plaintiff asserted that the infringing activity was driven by commercial purposes. 122 F.3d at 1027. The plaintiff alleged that the safe harbor did not apply because the defendant's actual purpose behind the testing was to "promote the [device] and other equipment to potential customers" and to offer it for sale. *Id.* The Federal Circuit rejected this argument, explaining that "section 271(e)(1) requires only that the otherwise infringing act be performed 'solely for uses reasonably related to' FDA approval." *Id*. at 1030. "The statute, therefore, does not look to the underlying purposes or attendant consequences of the activity . . . , as long as the use is reasonably related to FDA approval." *Id.* Because the device testing (the allegedly infringing act there) was reasonably related to obtaining FDA approval, the safe harbor applied, regardless of defendant's intent or purpose. *Id.* Therefore, the court's safe harbor analysis focused on uses, not "purposes" or "motives." *Id*. at 1278, 1280 ("Congress did not intend the availability of the exemption to turn on findings about a party's 'purposes' or 'motives'"); *see also Genentech*, 436 F. Supp. 2d at 1095 (even if accused experiments were conducted in part for "commercial reasons," the safe harbor

applied because "the experiments would produce information that would be given to the FDA in order to get FDA approval").

Similarly, Plaintiff contends that *Amgen Inc. v. Hospira, Inc*., 944 F.3d 1327 (Fed. Cir. 2019), stands for the proposition that that commercial intent can be probative of whether an activity is "reasonably related" to regulatory uses. Opp. at 12. In *Amgen*, a jury instruction correctly instructed the jury to focus on the allegedly infringing activity and whether that activity was reasonably related to the development and submission of information to the FDA. 944 F.3d at 1338-39 ("The jury instructions properly asked whether . . . each accused activity[] was for uses reasonably related to submitting information to the FDA."). Hospira objected to part of the jury instruction, which stated that "[i]f Hospira has proved that the manufacture of a particular batch was reasonably related to developing and submitting information to the FDA in order to obtain FDA approval, Hospira's additional underlying purposes for the manufacture and use of that batch do not remove that batch from the Safe Harbor defense." *Id*. at 1338. In finding no legal error with this jury instruction, the Federal Circuit in *Amgen* affirmed that "*underlying purposes do not matter* as long as Hospira proved that the manufacture of any given batch of drug substance [the accused activity] was *reasonably related to developing information for FDA submission*." *Id*. at 1339 (emphasis added).

Given this guidance from the Federal Circuit, the safe harbor inquiry here focuses only on Meril's allegedly infringing acts, specifically (1) shipping the Myval Samples to UW; and (2) transporting the Myval Samples to the TCT Conference. As discussed above, both acts fall squarely within the safe harbor. Transportation of the Myval Samples to UW was an exempt act because it generated preclinical data to support Meril's clinical trials. Likewise, transportation of the Myval Samples to the TCT Conference (with no sales or offers for sale) was an exempt act because Meril is a sponsor "responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing." *Telectronics II*, 982 F.2d at 1523 (citing 21 C.F.R. § 812.40). "[Meril's] intent or alternative uses are irrelevant to its qualification to invoke the section 271(e)(1) shield." *Abtox*, 122 F.3d at 1030. Accordingly, Defendants' underlying purposes are not relevant to the safe harbor inquiry, and the Court finds that

Defendants' transportation of the Myval System and Myval Samples to UW and the TCT conference fell within the safe harbor, such that there is no infringement.[7]

C. Rule 56(d) Motion

Plaintiff contends that there is an incomplete record regarding Meril's purportedly infringing acts, and that Meril's witnesses testified regarding plans surround the Landmark Trial, while Meril refused to produce documents relevant to this purported plan from earlier than May 2019.

A party seeking relief under Rule 56(d) must show "(1) that they have set forth in affidavit form the specific facts that they hope to elicit from further discovery, (2) that the facts sought exist, and (3) that these sought-after facts are essential to resist the summary judgment motion." *State of Cal., on Behalf of Cal. Dept. of Toxic Substances Control v. Campbell*, 138 F.3d 772, 780 (9th Cir. 1998). Plaintiff must have also diligently pursued the requested discovery. *See Conkle v. Jeong*, 73 F.3d 909, 914 (9th Cir. 1995).

In December 2019, Plaintiff served its first set of written discovery seeking broad categories of documents relating to all clinical trials for Myval. Mayer Reply Decl. ¶ 12. In April 2020, Plaintiff served a second set of written discovery, this time seeking broad categories of documents relating to the Landmark Trial. *Id.* ¶ 19. The parties met and conferred in late June, but it appears Plaintiff waited until July 27 to provide Meril with a draft motion to compel, which it filed after business hours on July 30, one business day before the first scheduled deposition. *Id.* Magistrate Judge Westmore denied Plaintiff's motion, holding that it was "unreasonable" to expect the Court to resolve the dispute on the "eve of deposition." Dkt. No. 77.

Plaintiff's failure to diligently pursue discovery is a sufficient basis to deny the Rule 56(d) motion. *Zamora v. City of Oakland*, No. 12-cv-02734 NC, 2013 WL 4103109, at *4 (N.D. Cal. Aug. 12, 2013) (plaintiff's failure to timely move to compel is ground for denying Rule 56(d) motion). Plaintiff contends that the majority of Meril's document production came after Meril

[7] Because intent and alternative uses are not relevant to the application of the safe harbor once it is determined that the allegedly infringing acts were reasonably related to FDA approval, the Court need not reach the issue of Meril's alleged commercial intent. *See Abtox*, 122 F.3d at 1030; *Amgen*, 944 F.3d at 1339.

moved for summary judgment, Opp. at 21, 25, but this appears to be a result of the Court's adoption of Plaintiff's proposed briefing schedule, which provided for subsequent written discovery after Meril moved for summary judgment. *See* Dkt. Nos. 52, 60; Mayer Reply Decl. ¶ 22. Finally, the timing of Meril's five document productions prior to the depositions also appears to be due, in part, to Plaintiff's delay. For example, on May 27, 2020, Meril disclosed the date ranges Meril used to search ESI and informed Plaintiff that Meril did not agree with Plaintiff's proposed date ranges. Mayer Reply Decl. ¶ 25, Ex. 23. Plaintiff did not raise this issue with Meril until July 15, 2020. Dkt. No. 72.

Accordingly, the Court **DENIES** Plaintiff's Rule 56(d) motion.

D. Motions to Seal

Meril seeks to seal a number of documents because they contain, characterize, or refer to highly confidential business information. In the Ninth Circuit, a party seeking to file documents under seal in connection with a dispositive motion must establish compelling reasons for doing so to rebut the presumption against public access. *See Foltz v. State Farm Mut. Auto. Ins. Co*., 331 F.3d 1122, 1136 (9th Cir. 2003). The Court will address each request briefly in turn.

i. Dkt. No. 66

Meril seeks to seal certain limited portions of Exhibits A and B to the Lad Declaration; the entirety of Exhibits C, D, I, and K to the Lad Declaration; certain limited portions of Meril's Corrected Memorandum of Law in support of the Summary Judgment Motion; and certain limited portions of the Lad Declaration. These documents contain sensitive proprietary information concerning Meril's clinical and regulatory strategies for the Myval System. The Court finds that this information is proprietary and meets the standard to file under seal. *See, e.g. Lucas v. Breg, Inc*., No. 15-cv-00258-BASNLS, 2016 WL 5464549, at *2 (S.D. Cal. Sept. 28, 2016) (sealing 510(k) premarket submission to the FDA addressing safety and effectiveness of device); *United States ex rel. Ruhe v. Masimo Corp*., No. 10-cv-08169-CJC(VBKx), 2013 WL 12131173, at *2 (C.D. Cal. Aug. 26, 2013) (internal research studies and clinical tests for developing the accused device, and non-public data submitted to the FDA in the course of regulatory approval, were "confidential, proprietary, and [ ] valuable"); *In re Incretin-Based Therapies Prods. Liab. Litig.*,

No.13md2452 AJB (MDD), 2015 WL 11658712, at *3 (S.D. Cal. Nov. 18, 2015) (sealing confidential and proprietary information relating to the "development, testing, and regulation" of proposed drugs, the disclosure of which would result in "significant competitive harm"); *Biovail Labs., Inc. v. Anchen Pharm., Inc*., 463 F. Supp. 2d 1073, 1083 (C.D. Cal. 2006) ("indisputable" that information contained in abbreviated new drug application to the FDA constituted trade secrets, the disclosure of which to a competitor would be "extremely damaging"). Accordingly, the Motion to Seal (Dkt. No. 66) is **GRANTED**.

ii. Dkt. Nos. 81 and 87

Plaintiff also seeks to file under seal certain information designated by Meril as "HIGHLY CONFIDENTIAL – OUTSIDE ATTORNEYS' EYES ONLY" under the Protective Order applicable in this case. Specifically, Plaintiff seeks to file under seal certain limited portions of Edwards' Opposition brief; certain limited portions of the Declaration of Matthew Stephens in Support of Edwards' Opposition; and the entirety of Exhibits A-E, K, 10, 13, 19, 21-23, 25-26, 29, 36-38, 40, 43-44, 47-48, 50, 51, 53, 55, and 57-59 to the Declaration of Matthews Stephens in Support of Edwards' Opposition. Plaintiff requests that the Court grant this administrative motion to the extent Defendants' information qualifies as "privileged, protectable as a trade secret, or otherwise entitled to protection under the law." However, the parties' designations alone are insufficient to meet the compelling reasons standard, and the Court therefore **DENIES** this request to seal. Dkt. No. 81.

In light of this, Defendants filed a motion to seal (Dkt. No. 87) to identify the limited items it seeks to seal, and to provide a revised proposed order and redacted documents reflecting these changes. Meril seeks to now seal the entirety of Exhibits A, B, C, E, K, 29, 36, 38, 43-44, 47-48, 50-51, 53, 55, 57-59 to the Declaration of Matthew Stephens In Support of Plaintiff's Opposition ("Stephens Declaration"; Dkt. No. 82-1). Meril contends that these documents contain sensitive proprietary information concerning Meril's clinical and regulatory strategies for its Myval System and its business strategies concerning trade shows. Meril also moves to file the following items under seal with more limited redactions than proposed in the prior motion to seal: certain limited portions of Exhibit D and 13 to the Stephens Declaration, and certain limited portions of

Plaintiff's Opposition brief and the Stephens Declaration that describe or reference the confidential documents as summarized above. These documents also contain sensitive proprietary information concerning Meril's clinical and regulatory strategies for its Myval System and its business strategy for trade conferences.

For the foregoing reasons, the Court finds that this information is proprietary and meets the standard to file under seal, and the Motion to Seal (Dkt. No. 87) is **GRANTED**.

iii. Dkt. No. 89

Finally, Meril seeks to seal certain limited portions of Exhibits 5, 7 and 8 to the Mayer Reply. Decl., the entirety of Exhibits 9-12 and 15 to the Mayer Reply Declaration, and certain limited portions of Meril's Reply. Meril contends that these documents contain sensitive proprietary information concerning Meril's clinical and regulatory strategies for the Landmark Trial, a clinical trial for Meril's proprietary Myval transcatheter heart valve and delivery system.

Exhibit 9 is an internal draft of Meril's trial synopsis for the Landmark Trial; Exhibits 10 and 11 are communications with clinical investigators regarding the design of the Landmark Trial; Exhibit 12 is Meril's supplemental presubmission to the FDA for the Landmark Trial as part of its process of receiving FDA approval for the Myval System; and Exhibit 15 is a report for a pre-clinical study for the Myval System. Exhibits 5, 7, and 8 are excerpts of deposition testimony that also describe Meril's confidential strategies for obtaining FDA approval for the Myval System. Exhibits 5, 7, and 8 also contain confidential business strategies for engaging clinicians at trade shows, which also meet the *Foltz* standard.

For the foregoing reasons, the Court finds that this information is proprietary and meets the standard to file under seal, and the Motion to Seal (Dkt. No. 89) is **GRANTED**.

IV. CONCLUSION

For the reasons discussed above, the Court **GRANTS** Defendants' Motion for Summary Judgment, and **GRANTS IN PART** and **DENIES IN PART** the Motions to Seal.

The claim construction hearing set for November 6, 2020 is **VACATED**. The Court **SETS** a further case management conference for November 3, 2020 to discuss the plan for promptly resolving the remaining causes of action. The parties shall file a case management statement, including a proposed case schedule, no later than October 27, 2020.

IT IS SO ORDERED.

Dated: October 16, 2020

HAYWOOD S. GILLIAM, JR.
United States District Judge

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA, OAKLAND DIVISION

EDWARDS LIFESCIENCES CORPORATION, a Delaware Corporation; EDWARDS LIFESCIENCES LLC, a Delaware Limited Liability Company,

Plaintiffs,

v.

MERIL LIFE SCIENCES PVT. LTD., an India private limited company; and MERIL, INC., a Delaware corporation,

Defendants.

Case No. 4:19-cv-06593 (HSG)
Hon. Haywood S. Gilliam, Jr.

JUDGMENT

Complaint filed: October 14, 2019
Trial Date: May 9, 2022

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD HEREIN:

WHEREAS Plaintiffs Edwards Lifesciences Corporation and Edwards Lifesciences LLC and Defendants Meril Life Sciences Pvt. Ltd. and Meril, Inc. have settled their dispute regarding Edwards' claims for statutory and common law trademark infringement, unfair competition under the Lanham Act, and unfair competition under California law (*See* Dkt. 51, Counts VI, VII and VIII) and have stipulated to dismiss them with prejudice.

GOOD CAUSE APPEARING, JUDGMENT IS HEREBY ENTERED against Plaintiffs Edwards Lifesciences Corporation and Edwards Lifesciences LLC and in favor of Defendants Meril Life Sciences Pvt. Ltd. and Meril, Inc. on Plaintiffs' Counts I, II, III, IV, and V for Patent Infringement consistent with the Court's Order re: Summary Judgment (Dkt. 98) pursuant to 28 U.S.C. § 1291 and Federal Rules of Civil Procedure 54 and 58.

Date: May 18, 2022

Honorable Haywood S. Gilliam, Jr.
United States District Judge

US010292817B2

(12) **United States Patent**
Hariton et al.

(10) **Patent No.: US 10,292,817 B2**
(45) **Date of Patent: May 21, 2019**

(54) **LOW PROFILE TRANSCATHETER HEART VALVE**

(71) Applicant: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(72) Inventors: **Ilia Hariton**, Zichron Yaacov (IL); **Netanel Benichou**, D.N. Hof HaCarmel (IL); **Yaacov Nitzan**, Kertzeliya (IL); **Bella Felsen**, Haifa (IL); **Diana Nguyen-Thien-Nhon**, Irvine, CA (US); **Rajesh A. Khanna**, Morrisdale, CA (US); **Son V. Nguyen**, Irvine, CA (US); **Tamir S. Levi**, Zikhron Yaakov (IL); **Itai Pelled**, Ramat-Hasharon (IL)

(73) Assignee: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/202,967**

(22) Filed: **Nov. 28, 2018**

(65) **Prior Publication Data**

US 2019/0099269 A1 Apr. 4, 2019

Related U.S. Application Data

(60) Continuation of application No. 15/984,716, filed on May 21, 2018, which is a continuation of application
(Continued)

(51) **Int. Cl.**
A61F 2/24 (2006.01)
A61F 2/95 (2013.01)

(52) **U.S. Cl.**
CPC ***A61F 2/2418*** (2013.01); ***A61F 2/2412*** (2013.01); ***A61F 2/2433*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC A61F 2/24; A61F 2/412; A61F 2/2418
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,409,013 A 11/1968 Berry
3,548,417 A 12/1970 Kisher
(Continued)

FOREIGN PATENT DOCUMENTS

DE 2246526 A1 3/1973
DE 19532846 A1 3/1997
(Continued)

OTHER PUBLICATIONS

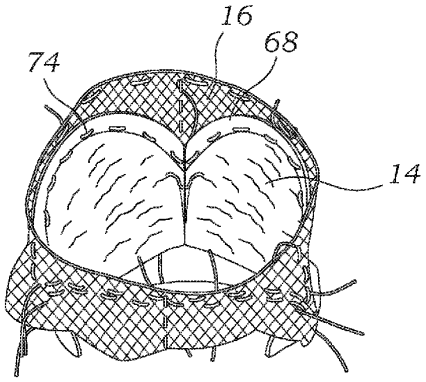
Andersen, et al., Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results withimplantation by catheter technique in closed chest pigs. European Heart Journal (1992), 13, 704-708.
(Continued)

Primary Examiner — Suzette J Gherbi
(74) *Attorney, Agent, or Firm* — Klarquist Sparkman, LLC; Joel B. German

(57) **ABSTRACT**

A method of crimping an implantable prosthetic valve can include placing protective material over at least a portion of the implantable prosthetic valve. The protective material can be configured to occupy space between open cells of a frame of the implantable prosthetic valve to prevent damage to a leaflet structure of the implantable prosthetic valve. The method can also include crimping the implantable prosthetic valve with the protective material on the implantable prosthetic valve, and removing the protective material from between the frame and the leaflet structure of the implantable prosthetic valve.

18 Claims, 15 Drawing Sheets



Related U.S. Application Data

No. 15/599,802, filed on May 19, 2017, now Pat. No. 9,974,652, which is a division of application No. 14/483,862, filed on Sep. 11, 2014, now Pat. No. 9,662,204, which is a continuation of application No. 13/897,036, filed on May 17, 2013, now abandoned, which is a continuation of application No. 13/167,549, filed on Jun. 23, 2011, now Pat. No. 8,454,685, which is a continuation of application No. 12/480,603, filed on Jun. 8, 2009, now Pat. No. 7,993,394.

(60) Provisional application No. 61/059,656, filed on Jun. 6, 2008.

(52) **U.S. Cl.**
CPC ***A61F 2/2475*** (2013.01); ***A61F 2/95*** (2013.01); *A61F 2002/9522* (2013.01); *A61F 2220/005* (2013.01); *A61F 2220/0033* (2013.01); *A61F 2220/0075* (2013.01); *A61F 2230/0054* (2013.01); *Y10T 29/49863* (2015.01)

(58) **Field of Classification Search**
USPC 623/2.11–2.19, 1.24
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,587,115	A	6/1971	Shiley	
3,657,744	A	4/1972	Ersek	
3,671,979	A	6/1972	Moulopoulos	
3,714,671	A	2/1973	Edwards et al.	
3,755,823	A	9/1973	Hancock	
4,035,849	A	7/1977	Angell et al.	
4,056,854	A	11/1977	Boretos et al.	
4,084,268	A *	4/1978	Ionescu	A61F 2/2409 623/2.15
4,106,129	A	8/1978	Carpentier et al.	
4,222,126	A	9/1980	Boretos et al.	
4,265,694	A	5/1981	Boretos et al.	
4,297,749	A	11/1981	Davis et al.	
RE30,912	E	4/1982	Hancock	
4,339,831	A	7/1982	Johnson	
4,343,048	A	8/1982	Ross et al.	
4,345,340	A	8/1982	Rosen	
4,373,216	A	2/1983	Klawitter	
4,406,022	A	9/1983	Roy	
4,441,216	A	4/1984	Ionescu et al.	
4,470,157	A	9/1984	Love	
4,535,483	A	8/1985	Klawitter et al.	
4,574,803	A	3/1986	Storz	
4,592,340	A	6/1986	Boyles	
4,605,407	A	8/1986	Black et al.	
4,612,011	A	9/1986	Kautzky	
4,643,732	A	2/1987	Pietsch et al.	
4,655,771	A	4/1987	Wallsten	
4,692,164	A	9/1987	Dzemeshkevich et al.	
4,733,665	A	3/1988	Palmaz	
4,759,758	A	7/1988	Gabbay	
4,762,128	A	8/1988	Rosenbluth	
4,777,951	A	10/1988	Cribier et al.	
4,787,899	A	11/1988	Lazarus	
4,787,901	A	11/1988	Baykut	
4,796,629	A	1/1989	Grayzel	
4,820,299	A	4/1989	Philippe et al.	
4,829,990	A	5/1989	Thuroff et al.	
4,851,001	A	7/1989	Taheri	
4,856,516	A	8/1989	Hillstead	
4,878,495	A	11/1989	Grayzel	
4,878,906	A	11/1989	Lindemann et al.	
4,883,458	A	11/1989	Shiber	
4,922,905	A	5/1990	Strecker	
4,966,604	A	10/1990	Reiss	
4,979,939	A	12/1990	Shiber	
4,986,830	A	1/1991	Owens et al.	
4,994,077	A	2/1991	Dobben	
5,007,896	A	4/1991	Shiber	
5,026,366	A	6/1991	Leckrone	
5,032,128	A	7/1991	Alonso	
5,037,434	A	8/1991	Lane	
5,047,041	A	9/1991	Samuels	
5,059,177	A	10/1991	Towne et al.	
5,080,668	A	1/1992	Bolz et al.	
5,085,635	A	2/1992	Cragg	
5,089,015	A	2/1992	Ross	
5,152,771	A	10/1992	Sabbaghian et al.	
5,163,953	A	11/1992	Vince	
5,167,628	A	12/1992	Boyles	
5,192,297	A	3/1993	Hull	
5,266,073	A	11/1993	Wall	
5,282,847	A	2/1994	Trescony et al.	
5,295,958	A	3/1994	Shturman	
5,332,402	A	7/1994	Teitelbaum	
5,360,444	A	11/1994	Kusuhara	
5,370,685	A	12/1994	Stevens	
5,397,351	A	3/1995	Pavcnik et al.	
5,411,055	A	5/1995	Kane	
5,411,552	A	5/1995	Andersen et al.	
5,443,446	A	8/1995	Shturman	
5,480,424	A	1/1996	Cox	
5,500,014	A	3/1996	Quijano et al.	
5,545,209	A	8/1996	Roberts et al.	
5,545,214	A	8/1996	Stevens	
5,549,665	A	8/1996	Vesely et al.	
5,554,185	A	9/1996	Block et al.	
5,558,644	A	9/1996	Boyd et al.	
5,571,175	A	11/1996	Vanney et al.	
5,584,803	A	12/1996	Stevens et al.	
5,591,185	A	1/1997	Kilmer et al.	
5,591,195	A	1/1997	Taheri et al.	
5,607,464	A	3/1997	Trescony et al.	
5,607,465	A *	3/1997	Camilli	A61F 2/2418 604/104
5,609,626	A	3/1997	Quijano et al.	
5,628,792	A	5/1997	Lentell	
5,639,274	A	6/1997	Fischell et al.	
5,665,115	A	9/1997	Cragg	
5,713,953	A *	2/1998	Vallana	A61F 2/2412 623/2.15
5,716,417	A	2/1998	Girard et al.	
5,728,068	A	3/1998	Leone et al.	
5,733,326	A *	3/1998	Tomonto	A61L 27/04 623/1.44
5,749,890	A	5/1998	Shaknovich	
5,756,476	A	5/1998	Epstein et al.	
5,769,812	A	6/1998	Stevens et al.	
5,800,508	A	9/1998	Goicoechea et al.	
5,840,081	A	11/1998	Andersen et al.	
5,855,597	A	1/1999	Jayaraman	
5,855,601	A	1/1999	Bessler et al.	
5,855,602	A	1/1999	Angell	
5,925,063	A	7/1999	Khosravi	
5,957,949	A	9/1999	Leonhardt et al.	
6,027,525	A	2/2000	Suh et al.	
6,132,473	A	10/2000	Williams et al.	
6,168,614	B1	1/2001	Andersen et al.	
6,171,335	B1	1/2001	Wheatley et al.	
6,174,327	B1	1/2001	Mertens et al.	
6,210,408	B1	4/2001	Chandrasekaran et al.	
6,217,585	B1	4/2001	Houser et al.	
6,221,091	B1	4/2001	Khosravi	
6,231,602	B1	5/2001	Carpentier et al.	
6,245,102	B1	6/2001	Jayaraman	
6,299,637	B1	10/2001	Shaolian et al.	
6,302,906	B1	10/2001	Goecoechea et al.	
6,338,740	B1	1/2002	Carpentier	
6,350,277	B1	2/2002	Kocur	
6,352,547	B1	3/2002	Brown et al.	
6,425,916	B1	7/2002	Garrison et al.	
6,440,164	B1 *	8/2002	DiMatteo	A61F 2/2412 623/1.24

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,454,799 B1 9/2002 Schreck
6,458,153 B1 * 10/2002 Bailey A61F 2/2418 623/1.24
6,461,382 B1 10/2002 Cao
6,468,660 B2 10/2002 Ogle et al.
6,482,228 B1 11/2002 Norred
6,488,704 B1 12/2002 Connelly et al.
6,503,272 B2 * 1/2003 Duerig A61F 2/2418 623/1.24
6,527,979 B2 3/2003 Constantz
6,562,069 B2 * 5/2003 Cai A61F 2/2412 623/2.12
6,569,196 B1 5/2003 Vesely
6,582,462 B1 6/2003 Andersen et al.
6,605,112 B1 8/2003 Moll et al.
6,652,578 B2 11/2003 Bailey et al.
6,689,123 B2 2/2004 Pinchasik
6,716,244 B2 4/2004 Klaco
6,730,118 B2 5/2004 Spenser et al.
6,733,525 B2 5/2004 Yang et al.
6,767,362 B2 7/2004 Schreck
6,769,161 B2 8/2004 Brown et al.
6,783,542 B2 8/2004 Eidenschink
6,830,584 B1 12/2004 Seguin
6,878,162 B2 4/2005 Bales et al.
6,893,460 B2 * 5/2005 Spenser A61F 2/2412 623/2.14
6,908,481 B2 6/2005 Cribier
6,918,929 B2 * 7/2005 Udipi A61L 31/10 427/2.25
6,936,067 B2 8/2005 Buchanan
7,018,406 B2 3/2006 Seguin et al.
7,018,408 B2 3/2006 Bailey et al.
7,096,554 B2 8/2006 Austin et al.
7,225,518 B2 6/2007 Eidenschink et al.
7,276,078 B2 10/2007 Spenser et al.
7,276,084 B2 10/2007 Yang et al.
7,316,710 B1 1/2008 Cheng et al.
7,318,278 B2 1/2008 Zhang et al.
7,374,571 B2 5/2008 Pease et al.
7,393,360 B2 7/2008 Spenser et al.
7,462,191 B2 12/2008 Spenser et al.
7,510,575 B2 3/2009 Spenser et al.
7,563,277 B2 * 7/2009 Case A61F 2/2418 427/2.24
7,563,280 B2 7/2009 Anderson et al.
7,585,321 B2 9/2009 Cribier
7,618,446 B2 11/2009 Andersen et al.
7,618,447 B2 11/2009 Case et al.
7,655,034 B2 2/2010 Mitchell et al.
7,785,366 B2 8/2010 Maurer et al.
7,959,665 B2 6/2011 Pienknagura
7,959,672 B2 6/2011 Salahieh et al.
7,993,394 B2 8/2011 Hariton et al.
8,029,556 B2 10/2011 Rowe
8,034,099 B2 * 10/2011 Pellegrini A61F 2/91 623/1.1
8,075,611 B2 12/2011 Millwee et al.
8,128,686 B2 3/2012 Paul et al.
8,167,932 B2 5/2012 Bourang
8,291,570 B2 * 10/2012 Eidenschink A61F 2/95 29/458
8,348,998 B2 1/2013 Pintor
8,449,606 B2 5/2013 Eliasen et al.
8,454,685 B2 * 6/2013 Hariton A61F 2/2412 623/2.17
8,652,203 B2 2/2014 Quadri
8,747,463 B2 6/2014 Fogarty et al.
2001/0021872 A1 9/2001 Bailey et al.
2002/0026094 A1 2/2002 Roth
2002/0032481 A1 3/2002 Gabbay
2002/0138135 A1 9/2002 Duerig et al.
2002/0143390 A1 10/2002 Ishii
2002/0173842 A1 11/2002 Buchanan
2003/0014105 A1 1/2003 Cao
2003/0050694 A1 3/2003 Yang et al.
2003/0100939 A1 5/2003 Yodfat et al.
2003/0158597 A1 8/2003 Quiachon et al.
2003/0212454 A1 11/2003 Scott et al.
2004/0024452 A1 2/2004 Kruse et al.
2004/0039436 A1 2/2004 Spenser et al.
2004/0078074 A1 4/2004 Anderson et al.
2004/0186558 A1 9/2004 Pavcnik et al.
2004/0186563 A1 9/2004 Lobbi
2004/0186565 A1 9/2004 Schreck
2004/0260389 A1 12/2004 Case et al.
2005/0010285 A1 2/2005 Lambrecht et al.
2005/0075725 A1 4/2005 Rowe
2005/0075728 A1 4/2005 Nguyen et al.
2005/0096736 A1 5/2005 Osse et al.
2005/0096738 A1 5/2005 Cali et al.
2005/0159811 A1 * 7/2005 Lane A61F 2/24
2005/0188525 A1 9/2005 Weber et al.
2005/0203614 A1 9/2005 Forster et al.
2005/0203617 A1 9/2005 Forster et al.
2005/0234546 A1 10/2005 Nugent et al.
2006/0004469 A1 * 1/2006 Sokel A61F 2/2415 29/516
2006/0025857 A1 2/2006 Bergheim et al.
2006/0058872 A1 3/2006 Salahieh et al.
2006/0074484 A1 4/2006 Huber
2006/0108090 A1 5/2006 Ederer et al.
2006/0149350 A1 7/2006 Patel et al.
2006/0183383 A1 8/2006 Asmus et al.
2006/0229719 A1 10/2006 Marquez et al.
2006/0259136 A1 11/2006 Nguyen et al.
2006/0259137 A1 11/2006 Artof et al.
2006/0287717 A1 12/2006 Rowe et al.
2007/0005131 A1 1/2007 Taylor
2007/0010876 A1 1/2007 Salahieh et al.
2007/0010877 A1 1/2007 Salahieh et al.
2007/0112422 A1 5/2007 Dehdashtian
2007/0162102 A1 7/2007 Ryan et al.
2007/0203503 A1 8/2007 Salahieh et al.
2007/0203575 A1 8/2007 Forster et al.
2007/0203576 A1 8/2007 Lee et al.
2007/0208550 A1 9/2007 Cao et al.
2007/0213813 A1 9/2007 von Segesser et al.
2007/0233228 A1 10/2007 Eberhardt et al.
2007/0260305 A1 11/2007 Drews et al.
2007/0265700 A1 11/2007 Eliasen et al.
2008/0114442 A1 5/2008 Mitchell et al.
2008/0125853 A1 5/2008 Bailey et al.
2008/0154355 A1 6/2008 Benichou et al.
2008/0021546 A1 7/2008 Patz et al.
2008/0183271 A1 7/2008 Frawley et al.
2008/0208327 A1 8/2008 Rowe
2008/0243245 A1 10/2008 Thamber et al.
2008/0255660 A1 10/2008 Guyenot et al.
2008/0275537 A1 11/2008 Limon
2008/0294248 A1 11/2008 Yang et al.
2009/0118826 A1 5/2009 Khaghani
2009/0125118 A1 * 5/2009 Gong A61F 2/0077 623/23.7
2009/0157175 A1 6/2009 Benichou
2009/0276040 A1 11/2009 Rowe
2009/0281619 A1 * 11/2009 Le A61M 25/01 623/2.11
2009/0287296 A1 11/2009 Manasse
2009/0287299 A1 11/2009 Tabor et al.
2009/0299452 A1 * 12/2009 Eidenschink A61F 2/95 623/1.11
2009/0319037 A1 12/2009 Rowe et al.
2010/0049313 A1 2/2010 Alon et al.
2010/0168844 A1 4/2010 Toomes et al.
2010/0185277 A1 4/2010 Braido et al.
2010/0082094 A1 7/2010 Quadri et al.
2010/0198347 A1 8/2010 Zakay et al.
2010/0204781 A1 8/2010 Alkhatib
2011/0015729 A1 1/2011 Jimenez et al.
2011/0022157 A1 1/2011 Essinger et al.
2011/0066224 A1 3/2011 White
2011/0137397 A1 6/2011 Chau et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2011/0218619	A1	9/2011	Benichou et al.	
2011/0319991	A1*	12/2011	Hariton	A61F 2/2412 623/2.14
2012/0089223	A1	4/2012	Nguyen et al.	
2012/0101571	A1	4/2012	Thamber et al.	
2012/0123529	A1	5/2012	Levi et al.	
2012/0259409	A1	10/2012	Nguyen et al.	
2013/0023985	A1	1/2013	Khairkhahan et al.	
2013/0046373	A1	2/2013	Cartledge et al.	
2013/0150956	A1	6/2013	Yohanan et al.	
2013/0166017	A1	6/2013	Cartledge et al.	
2013/0190857	A1	7/2013	Mitra et al.	
2013/0274873	A1	10/2013	Delaloye et al.	
2013/0310926	A1*	11/2013	Hariton	A61F 2/2412 623/2.11
2013/0317598	A1	11/2013	Rowe et al.	
2013/0331929	A1	12/2013	Mitra et al.	
2014/0194981	A1	7/2014	Menk et al.	
2014/0200661	A1	7/2014	Pintor et al.	
2014/0209238	A1*	7/2014	Bonyuet	A61F 2/2415 156/294
2014/0222136	A1	8/2014	Geist et al.	
2014/0277417	A1	9/2014	Schraut et al.	
2014/0277419	A1	9/2014	Garde et al.	
2014/0277424	A1	9/2014	Oslund	
2014/0277563	A1	9/2014	White	
2014/0296962	A1	10/2014	Cartledge et al.	
2014/0330372	A1	11/2014	Weston et al.	
2014/0343670	A1	11/2014	Bakis et al.	
2014/0343671	A1	11/2014	Yohanan et al.	
2014/0350667	A1	11/2014	Braido et al.	
2015/0073545	A1	3/2015	Braido	
2015/0073546	A1	3/2015	Braido	
2015/0135506	A1	5/2015	White	
2015/0157455	A1	6/2015	Hoang et al.	
2017/0014229	A1	1/2017	Nguyen-Then-Nhon et al.	
2018/0028310	A1	2/2018	Gurovich et al.	
2018/0153689	A1	6/2018	Maimon et al.	
2018/0325665	A1	11/2018	Gurovich et al.	
2018/0344456	A1	12/2018	Barash et al.	

FOREIGN PATENT DOCUMENTS

DE	19546692	A1	6/1997
DE	19857887	A1	7/2000
DE	19907646	A1	8/2000
DE	10049812	A1	4/2002
DE	10049813	C1	4/2002
DE	10049814	A1	4/2002
DE	10049815	A1	4/2002
EP	0103546	A1	3/1984
EP	0592410	A1	4/1994
EP	0597967	A1	5/1994
EP	0850607	A1	7/1998
EP	1057460	A1	12/2000
EP	1088529	A2	4/2001
EP	1570809	A1	9/2005
EP	1796597	A2	6/2007
FR	2788217	A1	7/2000
FR	2815844	A1	5/2002
GB	2056023		3/1981
SU	1271508	A1	11/1986
WO	1991017720	A1	11/1991
WO	1992017118	A1	10/1992
WO	1993001768	A1	2/1993
WO	1997024080	A1	7/1997
WO	1998029057	A1	7/1998
WO	1999030646	A1	6/1999
WO	1999033414	A1	7/1999
WO	1999040964	A1	9/1999
WO	1999047075	A1	9/1999
WO	2000018333	A1	4/2000
WO	2000041652	A1	7/2000
WO	2000047139	A1	8/2000
WO	2001035878	A2	5/2001
WO	2001049213	A2	7/2001
WO	2001054624	A1	8/2001
WO	2001054625	A1	8/2001
WO	2001062189	A1	8/2001
WO	2001064137	A1	9/2001
WO	2001076510	A2	10/2001
WO	2002022054	A1	3/2002
WO	2002036048	A1	5/2002
WO	2002041789	A2	5/2002
WO	2002043620	A1	6/2002
WO	2002047575	A2	6/2002
WO	2002049540	A2	6/2002
WO	2003047468	A1	6/2003
WO	2005034812	A1	4/2005
WO	2005055883	A2	6/2005
WO	2005084595	A1	9/2005
WO	2005102015	A2	11/2005
WO	2006014233	A2	2/2006
WO	2006032051		3/2006
WO	2006034008	A2	3/2006
WO	2006111391	A1	10/2006
WO	2006127089	A1	11/2006
WO	2006138173	A2	12/2006
WO	2007047488	A2	4/2007
WO	2007067942	A1	6/2007
WO	2007097983	A2	8/2007
WO	2008005405	A2	1/2008
WO	2008015257		2/2008
WO	2008035337	A2	3/2008
WO	2008091515	A2	7/2008
WO	2008147964		12/2008
WO	2008150529	A1	12/2008
WO	2009033469	A2	3/2009
WO	2009042196		4/2009
WO	2009053497		4/2009
WO	2009061389		5/2009
WO	2009116041		9/2009
WO	2009149462		12/2009
WO	2010011699		1/2010
WO	2010121076	A2	10/2010
WO	2013106585		7/2013
WO	2015085218		6/2015

OTHER PUBLICATIONS

Andersen, Henning Rud, History of Percutaneous Aortic Valve Prosthesis, Herz 34 2009 Nr. 5, Urban & Vogel, pp. 343-346, Skejby University Hospital Department of Cardiology, Aarhus, Denmark.

Pavcnik, et al. "Development and initial Experimental Evaluation of a Prosthetic Aortic Valve for Transcatheter Placement," Cardiovascular Radiology, vol. 183, No. 1. pp. 151-154. 1992.

Bailey, S. "Percutaneous Expandable Prosthetic Valves," Textbook of Interventional Cardiology vol. 2, 2nd Ed. pp. 1268-1276. 1994.

Al-Khaja, et al. "Eleven Years' Experience with Carpentier-Edwards Biological Valves in Relation to Survival and Complications," European Journal of Cardiothoracic Surgery, vol. 3. pp. 305-311. 1989.

Ross, "Aortic Valve Surgery," At a meeting of the Council on 4th Aug. 1966. pp. 192-197.

Sabbah, et al. "Mechanical Factors in the Degeneration of Porcine Bioprosthetic Valves: An Overview," Journal of Cardiac Surgery, vol. 4, No. 4. pp. 302-309. 1989.

Wheatley, "Valve Prostheses," Operative Surgery, 4th ed. pp. 415-424. 1986.

Uchida, "Modifications of Gianturco Expandable Wire Stents," American Journal of Roentgenology, vol. 150. pp 1185-1187. 1986.

* cited by examiner

Fig. 1

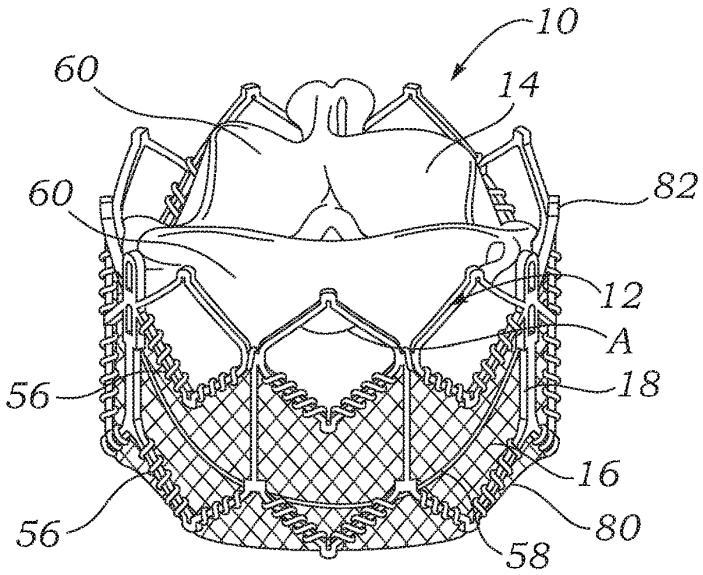


Fig. 2

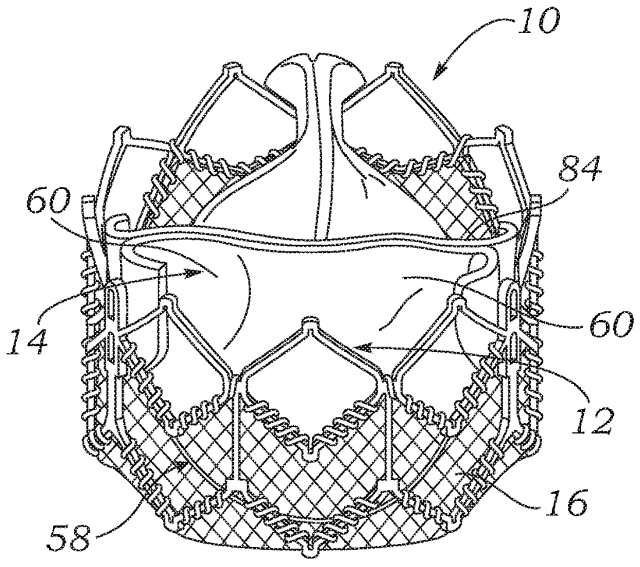


Fig. 3

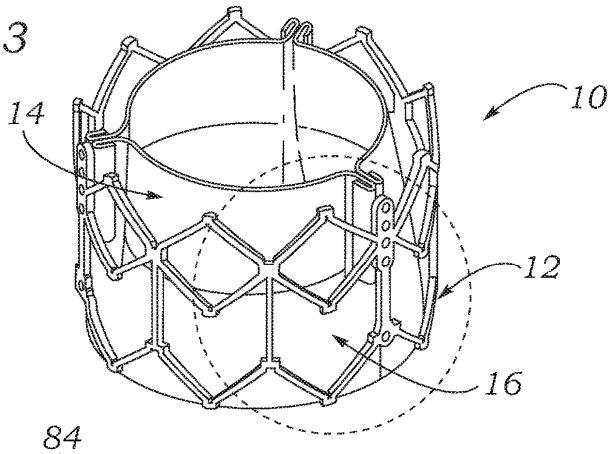


Fig. 4

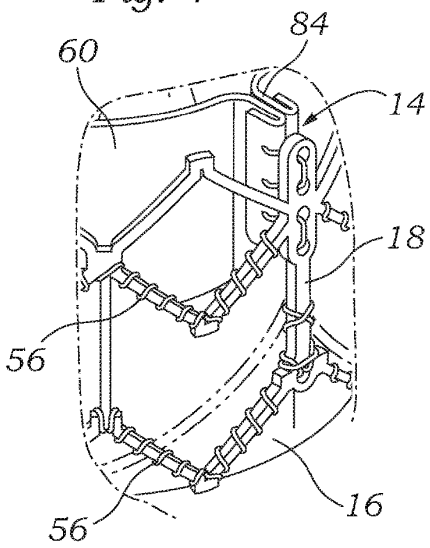


Fig. 5

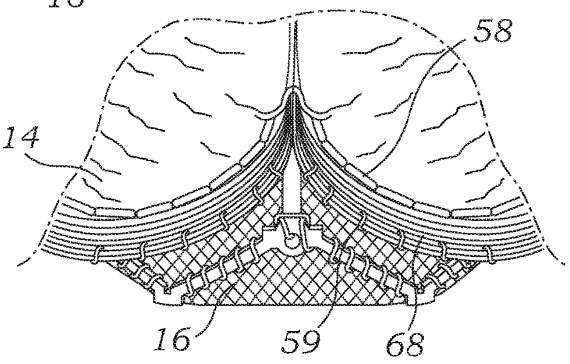


Fig. 6

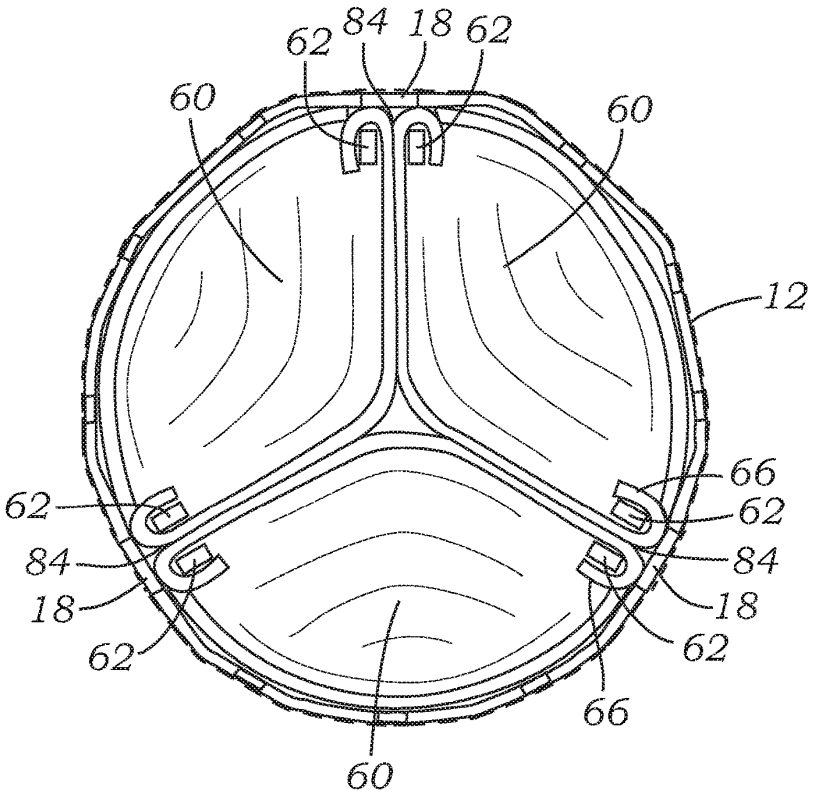


Fig. 12

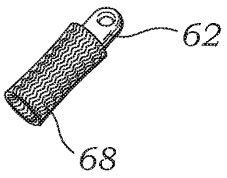


Fig. 13

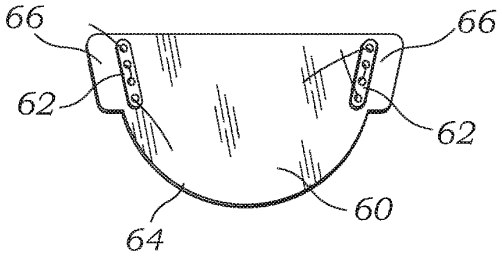


Fig. 14

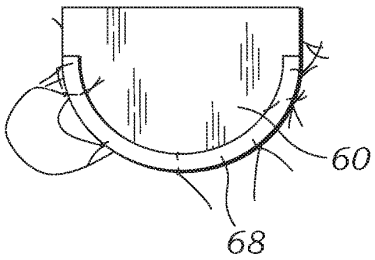


Fig. 15

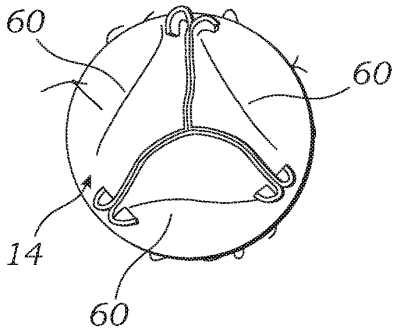


Fig. 6A

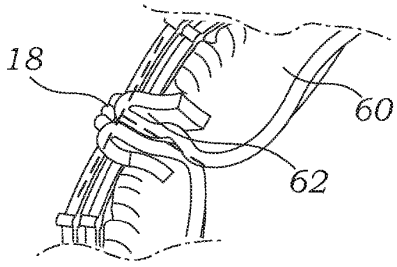


Fig. 7

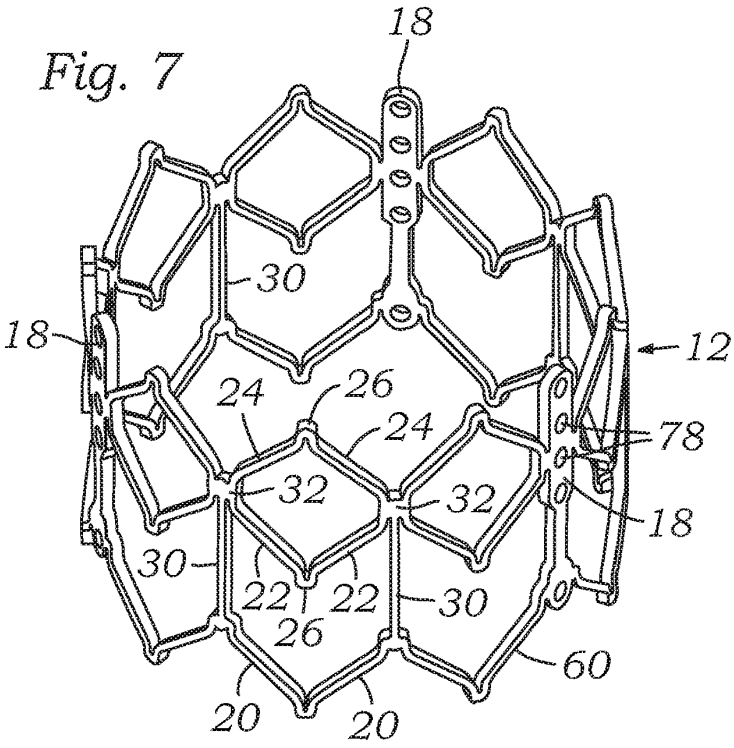


Fig. 8

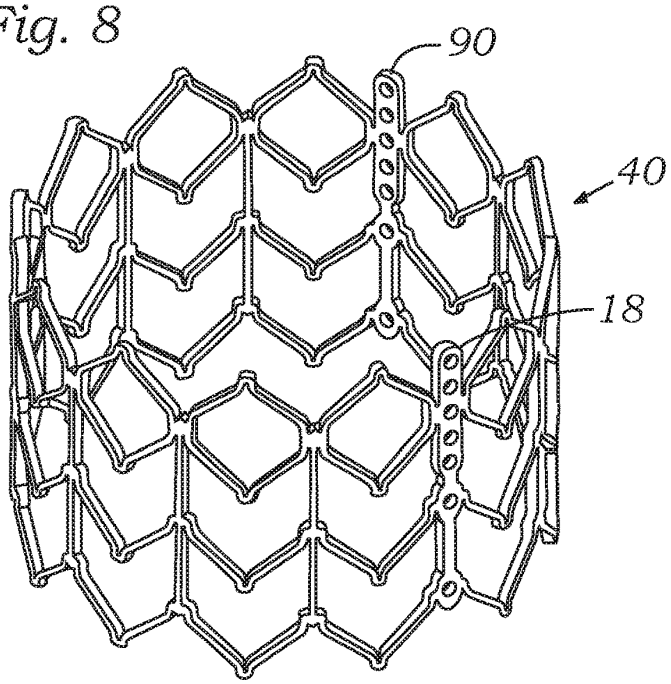


Fig. 9

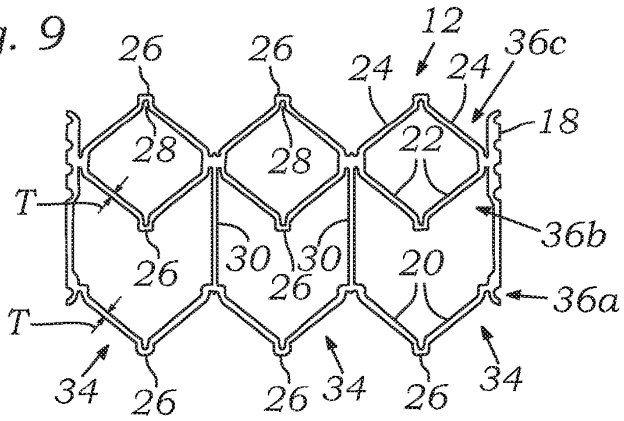


Fig. 10

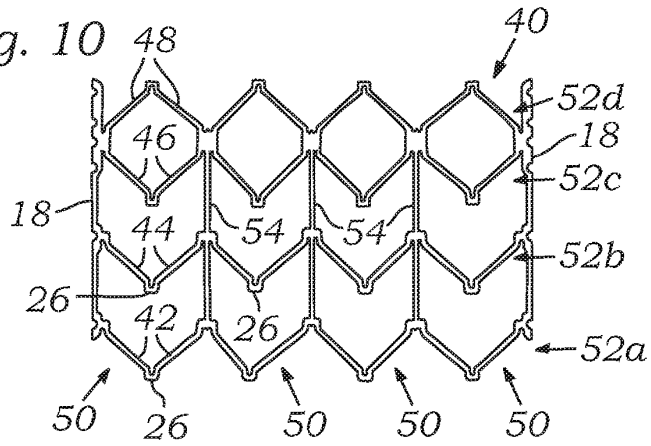


Fig. 11

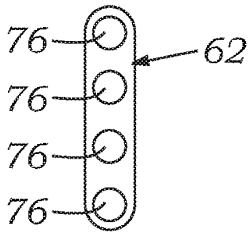


Fig. 16

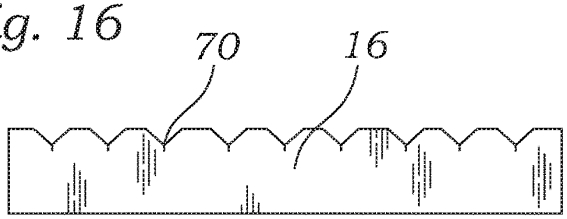


Fig. 17

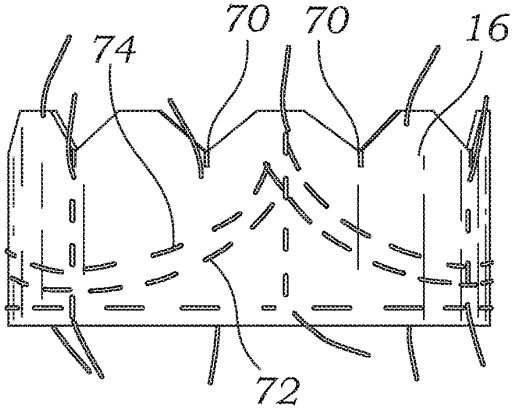


Fig. 18

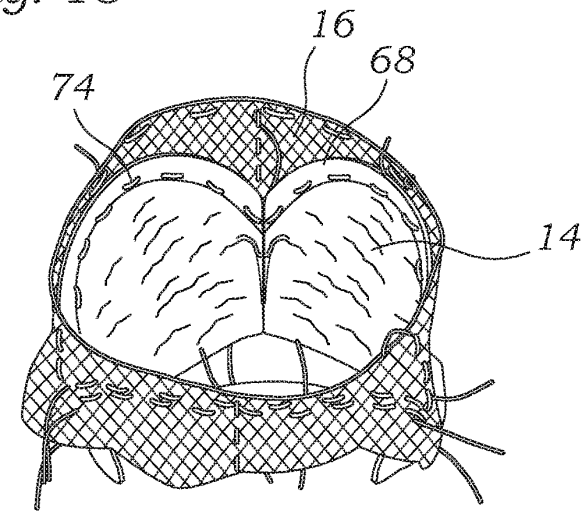


Fig. 19

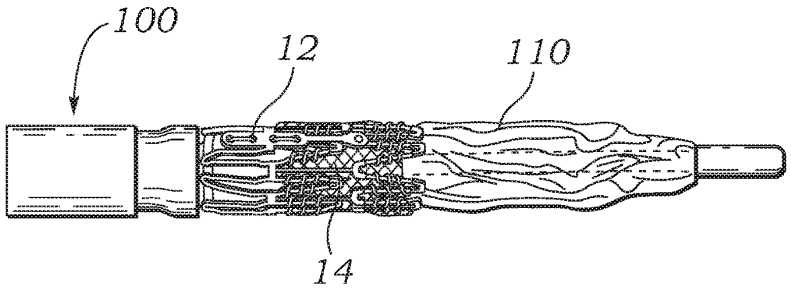


Fig. 20

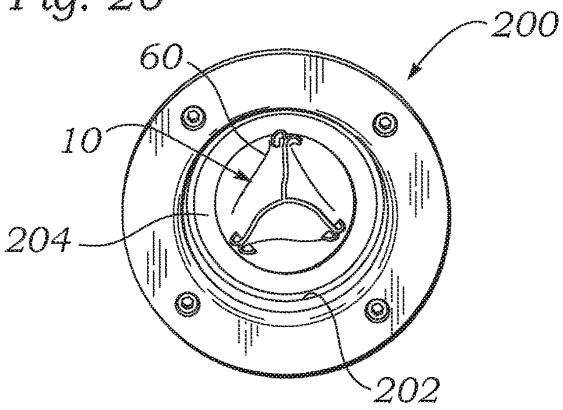


Fig. 21

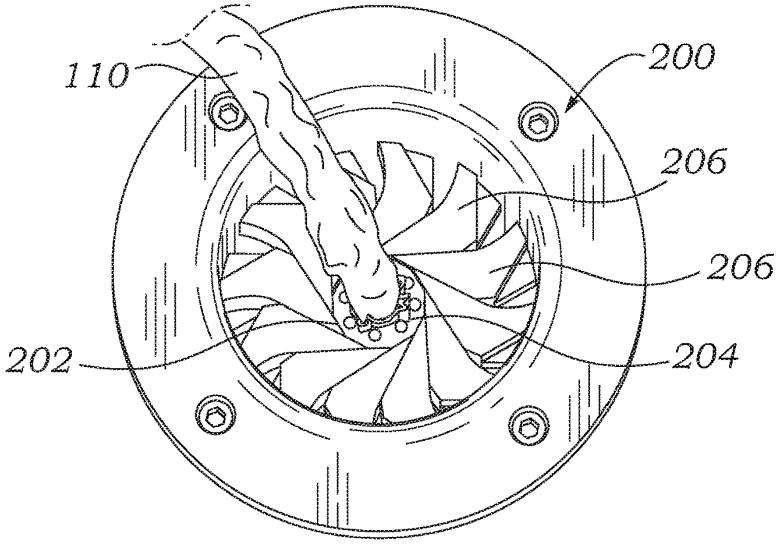


Fig. 22

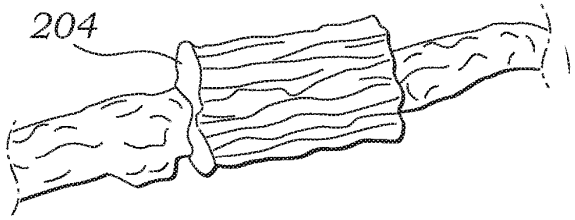


Fig. 23

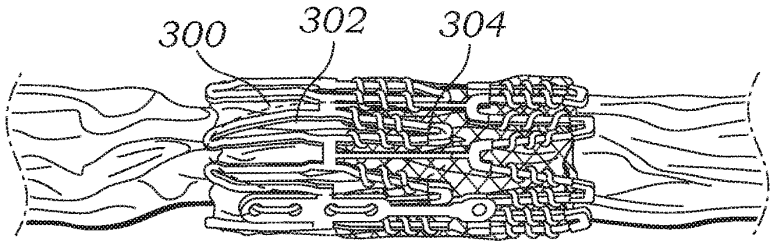


Fig. 24

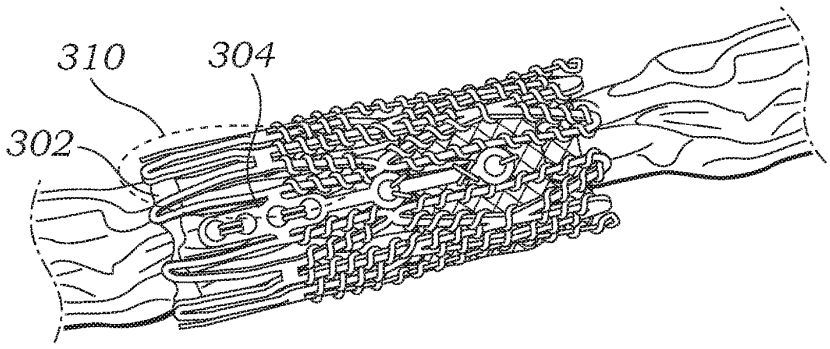


Fig. 25

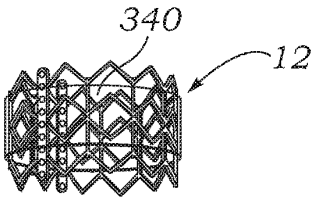


Fig. 26

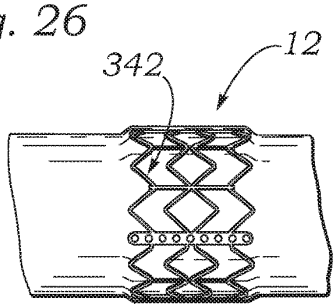


Fig. 27

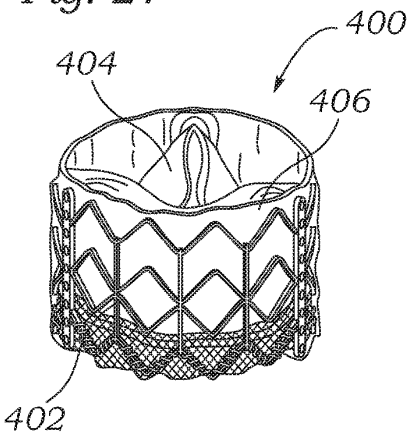


Fig. 28

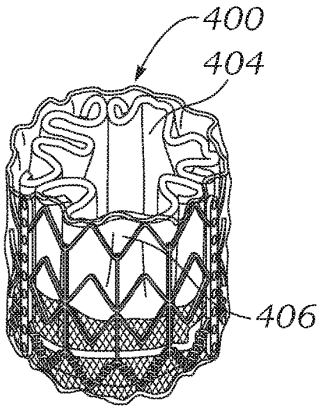


Fig. 29

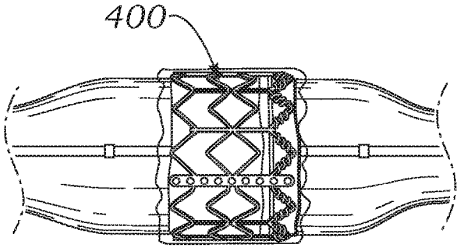


Fig. 30A

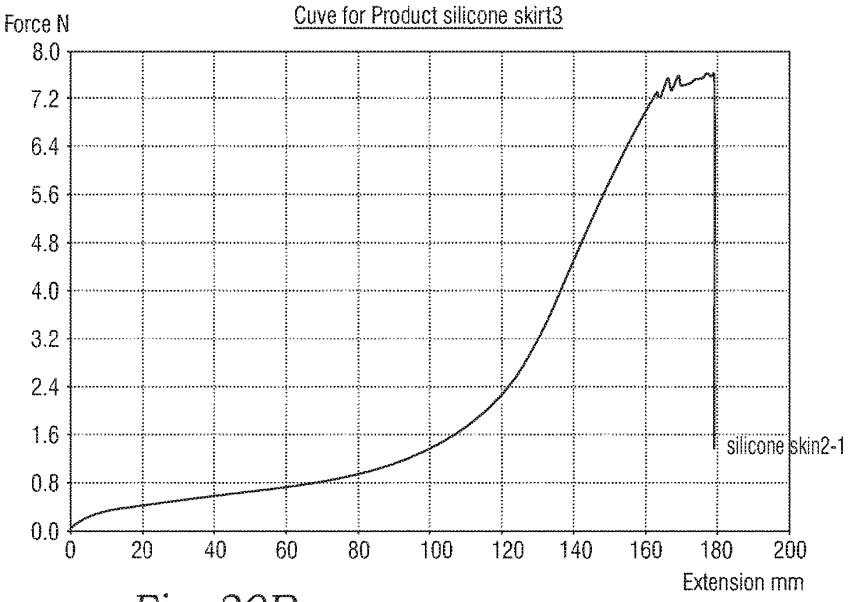


Fig. 30B

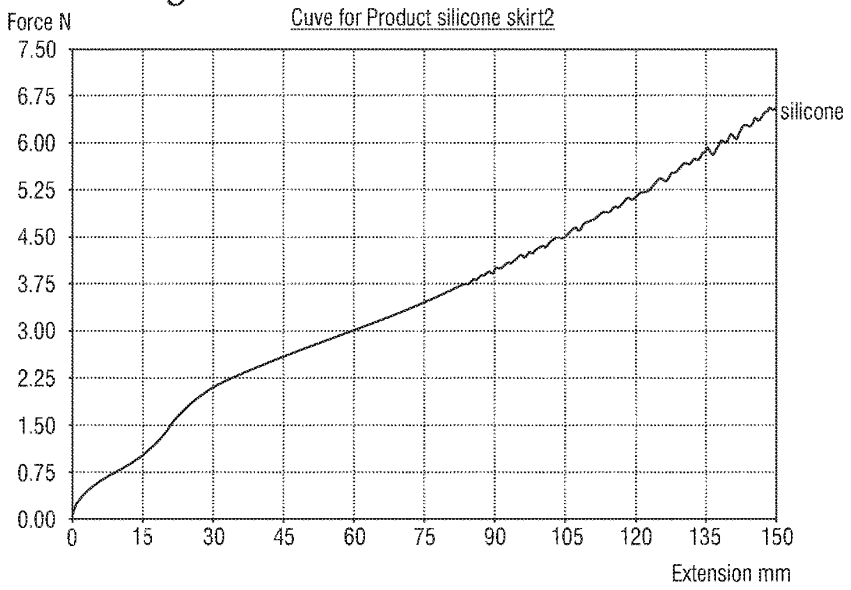


Fig. 30C

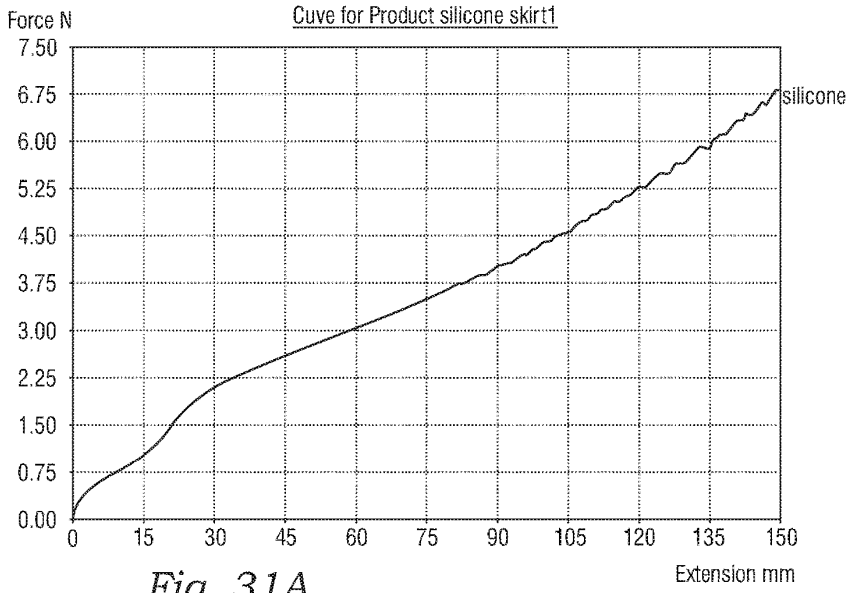


Fig. 31A

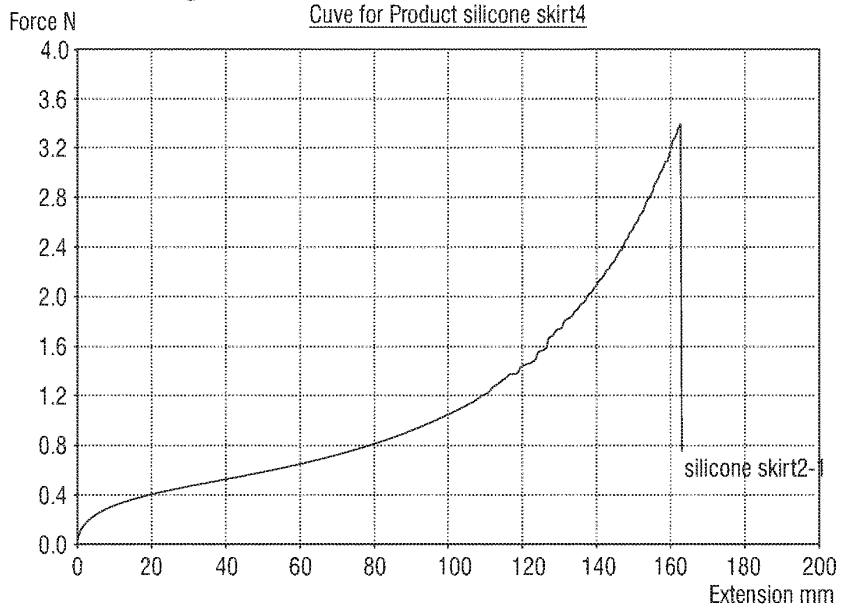


Fig. 31B

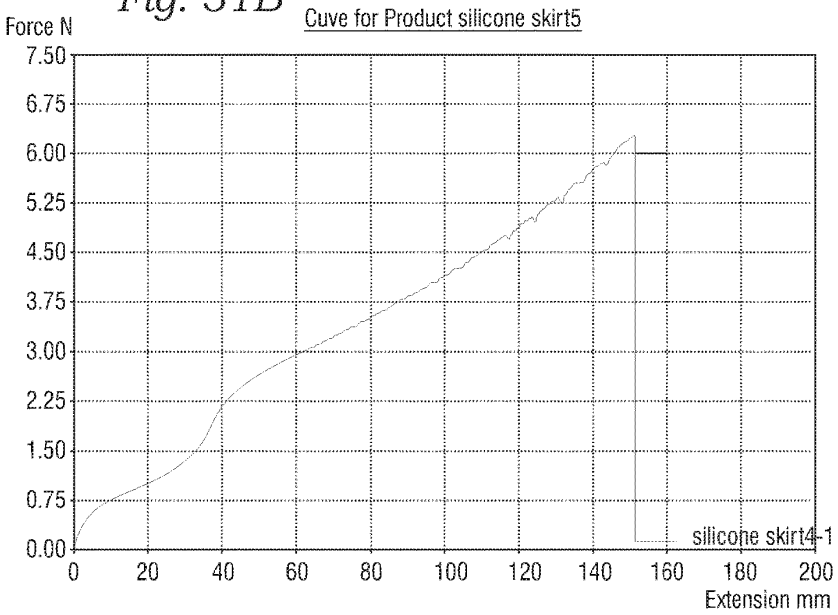


Fig. 31C

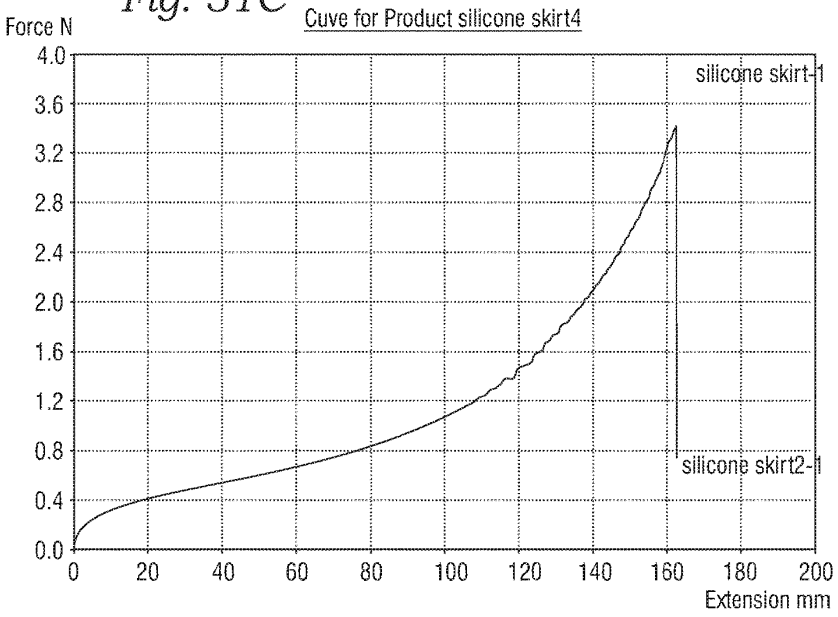


Fig. 31D

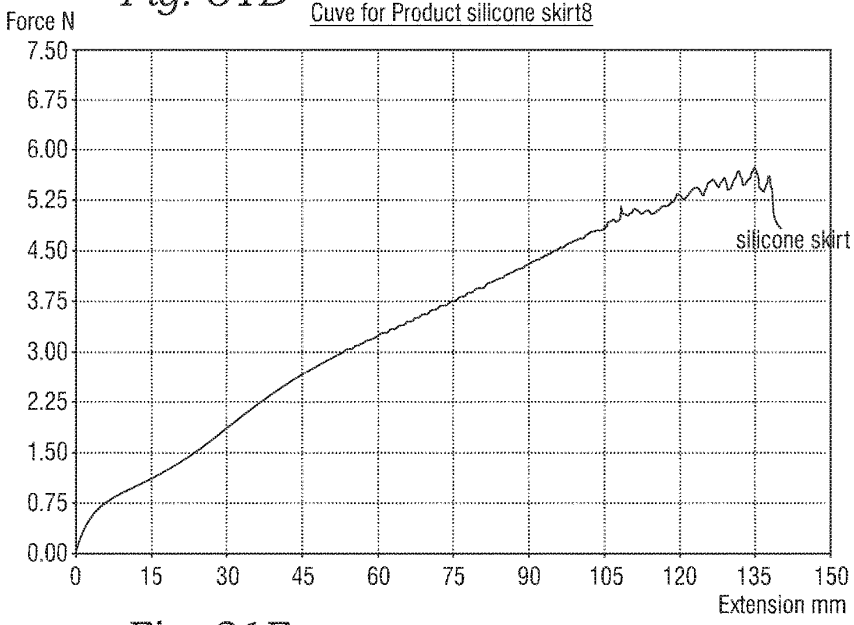


Fig. 31E

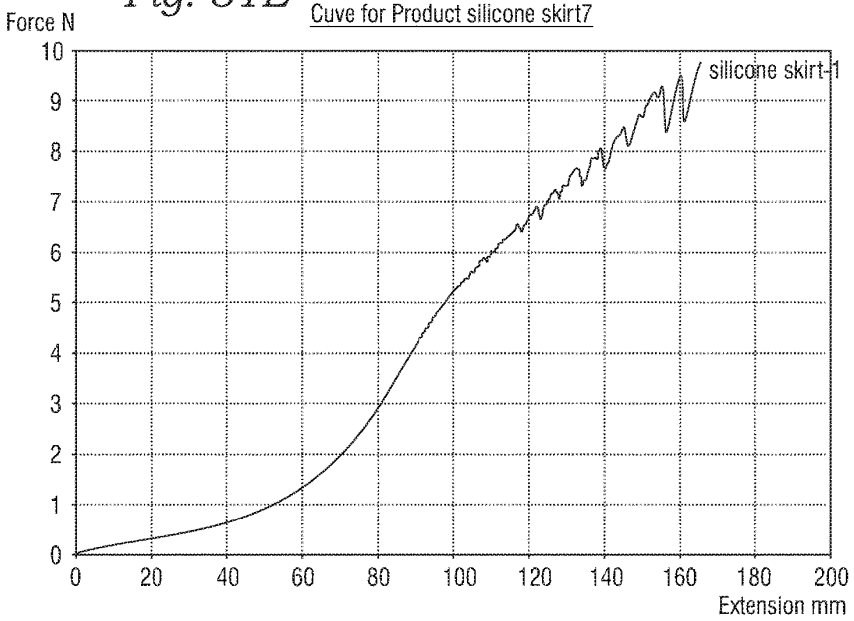
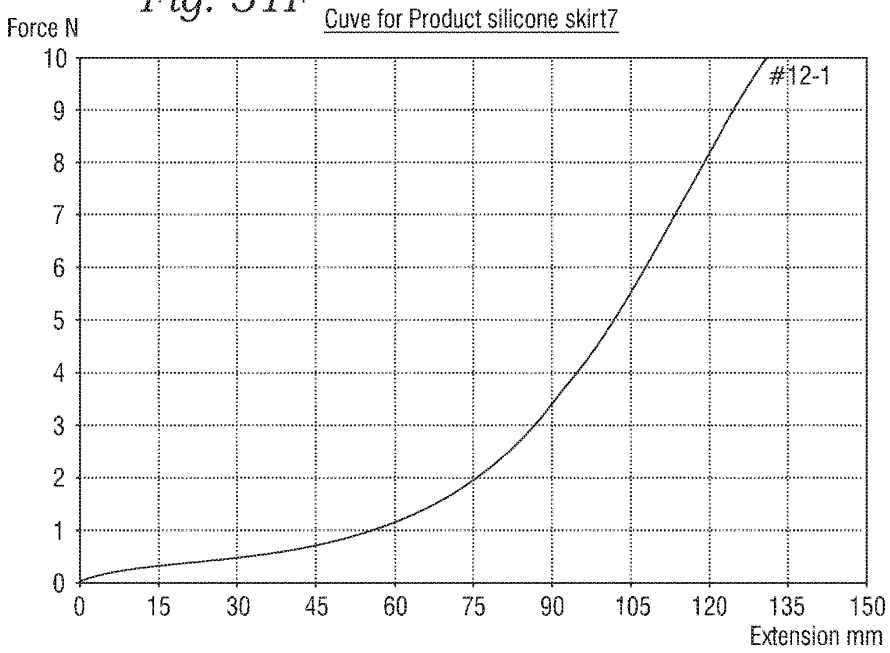


Fig. 31F


Cuve for Product silicone skirt7
Force N
10
9
8
7
6
5
4
3
2
1
0
#12-1
0
15
30
45
60
75
90
105
120
135
150
Extension mm

LOW PROFILE TRANSCATHETER HEART VALVE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/984,716, filed May 21, 2018, which is a continuation of U.S. patent application Ser. No. 15/599,802, filed May 19, 2017, now U.S. Pat. No. 9,974,652, which is a divisional of U.S. patent application Ser. No. 14/483,862, filed Sep. 11, 2014, now U.S. Pat. No. 9,662,204, which is a continuation of U.S. patent application Ser. No. 13/897,036, filed May 17, 2013, now abandoned, which is a continuation of U.S. patent application Ser. No. 13/167,549, filed Jun. 23, 2011, now U.S. Pat. No. 8,454,685, which is a continuation of U.S. patent application Ser. No. 12/480,603, filed Jun. 8, 2009, now U.S. Pat. No. 7,993,394, which claims the benefit of U.S. Patent Application No. 61/059,656, filed Jun. 6, 2008, the entire disclosures of which are incorporated herein by reference.

FIELD

The present disclosure relates to implantable devices and, more particularly, to valve prosthetics for implantation into body ducts, such as native heart valve annuluses.

DESCRIPTION OF THE RELATED ART

The human heart can suffer from various valvular diseases. These valvular diseases can result in significant malfunctioning of the heart and ultimately require replacement of the native valve with an artificial valve. There are a number of known artificial valves and a number of known methods of implanting these artificial valves in humans.

Various surgical techniques may be used to repair a diseased or damaged valve. In a valve replacement operation, the damaged leaflets are excised and the annulus sculpted to receive a replacement valve. Due to aortic stenosis and other heart valve diseases, thousands of patients undergo surgery each year wherein the defective native heart valve is replaced by a prosthetic valve, either bioprosthetic or mechanical. Another less drastic method for treating defective valves is through repair or reconstruction, which is typically used on minimally calcified valves. The problem with surgical therapy is the significant insult it imposes on these chronically ill patients with high morbidity and mortality rates associated with surgical repair.

When the valve is replaced, surgical implantation of the prosthetic valve typically requires an open-chest surgery during which the heart is stopped and patient placed on cardiopulmonary bypass (a so-called "heart-lung machine"). In one common surgical procedure, the diseased native valve leaflets are excised and a prosthetic valve is sutured to the surrounding tissue at the valve annulus. Because of the trauma associated with the procedure and the attendant duration of extracorporeal blood circulation, some patients do not survive the surgical procedure or die shortly thereafter. It is well known that the risk to the patient increases with the amount of time required on extracorporeal circulation. Due to these risks, a substantial number of patients with defective valves are deemed inoperable because their condition is too frail to withstand the procedure. By some estimates, more than 50% of the subjects suffering from aortic stenosis who are older than 80 years cannot be operated on for aortic valve replacement.

Because of the drawbacks associated with conventional open-heart surgery, percutaneous and minimally-invasive surgical approaches are garnering intense attention. In one technique, a prosthetic valve is configured to be implanted in a much less invasive procedure by way of catheterization. For instance, U.S. Pat. Nos. 5,411,522 and 6,730,118, which are incorporated herein by reference, describe collapsible transcatheter heart valves that can be percutaneously introduced in a compressed state on a catheter and expanded in the desired position by balloon inflation or by utilization of a self-expanding frame or stent.

An important design parameter of a transcatheter heart valve is the diameter of the folded or crimped profile. The diameter of the crimped profile is important because it directly influences the physician's ability to advance the valve through the femoral artery or vein. More particularly, a smaller profile allows for treatment of a wider population of patients, with enhanced safety.

SUMMARY

The present disclosure is directed toward new and non-obvious methods and apparatuses relating to prosthetic valves, such as heart valves.

In one representative embodiment, an implantable prosthetic valve comprises a radially collapsible and expandable frame, or stent, and a leaflet structure comprising a plurality of leaflets. The leaflet structure has a scalloped lower edge portion that is positioned inside of and secured to the frame. The valve can further include an annular skirt member, which can be disposed between the frame and the leaflet structure such that the scalloped lower edge portion can be attached to an inner surface of the skirt member. Each leaflet can have an upper edge, a curved lower edge and two side flaps extending between respective ends of the upper edge and the lower edge, wherein each side flap is secured to an adjacent side flap of another leaflet to form commissures of the leaflet structure. Each commissure can be attached to one of the commissure attachment posts, and a reinforcing bar can be positioned against each side flap for reinforcing the attachments between the commissures and the commissure attachment posts.

The frame can comprise a plurality of angularly spaced, axial struts that are interconnected by a plurality of rows of circumferential struts. Each row of circumferential struts desirably includes struts arranged in a zig-zag or saw-tooth pattern extending around the circumference of the frame.

In certain embodiments, at least one row, and preferably all rows, of circumferential struts include pairs of circumferential struts extending between two axial struts. Each strut of the pair has one end connected to a respective axial strut and another end interconnected to an adjacent end of the other strut of the same pair by a crown portion such that a gap exists between the adjacent ends of the struts. The angle between the struts of each pair desirably is between about 90 and 110 degrees, with about 100 degrees being a specific example. The frame desirably is made of a nickel-cobalt based alloy, such as a nickel cobalt chromium molybdenum alloy (e.g., MP35N™).

In another representative embodiment, an implantable prosthetic valve comprises a radially collapsible and expandable annular frame and a leaflet structure supported by the frame. The frame can comprise a plurality of interconnected struts defining a plurality of open cells in the frame. The valve further includes an annular cover member disposed on and covering the cells of at least a portion of the frame. The cover member desirably comprises an elastomer,

such as silicon, that can expand and stretch when the valve is expanded from a crimped state to an expanded state.

The cover member may be a thin sleeve of silicon that surrounds at least a portion of the frame. Alternatively, the cover member may be formed by dipping at least a portion of the frame in silicon or another suitable elastomer in liquefied form.

In another representative embodiment, a method is disclosed for crimping an implantable prosthetic valve having a frame and leaflets supported by the frame. The method comprises placing the valve in the crimping aperture of a crimping device such that a compressible material is disposed between the crimping jaws of the crimping device and the frame of the valve. Pressure is applied against the compressible material and the valve with the crimping jaws to radially crimp the valve to a smaller profile and compress the compressible material against the valve such that the compressible material extends into open cells of the frame and pushes the leaflets away from the inside of the frame.

The foregoing and other features and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a perspective view of a representative embodiment of a prosthetic heart valve.

FIG. **2** is another perspective view of the prosthetic valve of FIG. **1**.

FIG. **3** is another perspective view of the prosthetic valve of FIG. **1**.

FIG. **4** is an enlarged view of a section of the valve shown in FIG. **3**.

FIG. **5** is a bottom perspective view of the prosthetic valve of FIG. **1** showing the inside of the valve.

FIG. **6** is a top plan view of the prosthetic valve of FIG. **1**.

FIG. **6**A is an enlarged partial top view of the valve of FIG. **1** illustrating the positioning of the reinforcing bars with respect to the commissure attachment posts of the frame.

FIG. **7** is a perspective view of the frame of the prosthetic valve of FIG. **1**.

FIG. **8** is a perspective view of an alternative embodiment of a frame that can be used in the prosthetic valve of FIG. **1**.

FIG. **9** is a flattened view of 120-degree segment of the frame shown in FIG. **7**.

FIG. **10** is a flattened view of 120-degree segment of the frame shown in FIG. **8**.

FIG. **11** is a front view of a reinforcing bar that can be used to reinforce the connection of the valve leaflets to a frame in a prosthetic valve such as shown in FIG. **1**.

FIG. **12** is a perspective view of the reinforcing bar of FIG. **11** and a PET sleeve that can be used to cover the bar.

FIG. **13** is a flattened view of a leaflet of the valve shown in FIG. **1**.

FIG. **14** is a flattened view of the opposite side of the leaflet showing a reinforcing strip secured adjacent the bottom edge of the leaflet.

FIG. **15** is a top plan view of the leaflet structure of the valve of FIG. **1** prior to attachment to the frame.

FIG. **16** is a flattened view of the skirt used in the valve shown in FIG. **1**.

FIG. **17** is a side view of the skirt illustrating suture lines for attaching the skirt to the leaflet structure.

FIG. **18** is a bottom perspective view of the leaflet structure connected to the skirt so as to form a leaflet assembly.

FIG. **19** is a side view of a balloon catheter and a prosthetic valve crimped onto the balloon of the balloon catheter.

FIG. **20** is a front view of a crimping device showing a prosthetic valve positioned in the crimping aperture of the crimping device with a protective sleeve disposed between the valve and the crimping jaws.

FIG. **21** is a front view of the crimping device shown after the crimping jaws are forced inwardly to compress the valve and the protective sleeve.

FIG. **22** is a side view of the valve and protective sleeve after removal from the crimping device.

FIG. **23** is a side view of a prosthetic valve that has been crimped onto a balloon of a balloon catheter without a protective sleeve.

FIG. **24** is a side view of a prosthetic valve that has been crimped onto a balloon of a balloon catheter using a protective sleeve in the manner shown in FIGS. **20**-**21**.

FIG. **25** is a side view of a frame for a prosthetic valve having a silicon skirt, or sleeve, disposed on the outside of the frame.

FIG. **26** is a side view of a frame for a prosthetic valve having a silicon encapsulating layer covering the inside and outside of the frame.

FIG. **27** is a perspective view of a prosthetic valve comprising a frame having a silicon encapsulating layer.

FIG. **28** is a perspective view of the valve of FIG. **27** after it has been crimped to a smaller diameter.

FIG. **29** is a side view of the valve of FIG. **27** after it has been expanded by a balloon catheter.

FIGS. **30**A-**30**C are graphs illustrating the results of respective uniaxial tests performed on respective silicon test strips.

FIGS. **31**A-**31**F are graphs illustrating the results of respective uniaxial tests performed on respective silicon test strips having deliberately introduced tears.

DETAILED DESCRIPTION

FIGS. **1** and **2** illustrate an implantable prosthetic valve **10**, according to one embodiment. Valve **10** in the illustrated embodiment generally comprises a frame, or stent, **12**, a leaflet structure **14** supported by the frame, and a skirt **16** secured to the outer surface of the leaflet structure. Valve **10** typically is implanted in the annulus of the native aortic valve but also can be adapted to be implanted in other native valves of the heart or in various other ducts or orifices of the body. Valve **10** has a "lower" end **80** and an "upper" end **82**. In the context of the present application, the terms "lower" and "upper" are used interchangeably with the terms "inflow" and "outflow", respectively. Thus, for example, the lower end **80** of the valve is its inflow end and the upper end **82** of the valve is its outflow end.

Valve **10** and frame **12** are configured to be radially collapsible to a collapsed or crimped state for introduction into the body on a delivery catheter and radially expandable to an expanded state for implanting the valve at a desired location in the body (e.g., the native aortic valve). Frame **12** can be made of a plastically-expandable material that permits crimping of the valve to a smaller profile for delivery and expansion of the valve using an expansion device such as the balloon of a balloon catheter. Exemplary plastically-expandable materials that can be used to form the frame are described below. Alternatively, valve **10** can be a so-called

self-expanding valve wherein the frame is made of a self-expanding material such as Nitinol. A self-expanding valve can be crimped to a smaller profile and held in the crimped state with a restraining device such as a sheath covering the valve. When the valve is positioned at or near the target site, the restraining device is removed to allow the valve to self-expand to its expanded, functional size.

Referring also to FIG. **7** (which shows the frame alone for purposes of illustration), frame **12** is an annular, stent-like structure having a plurality of angularly spaced, vertically extending, commissure attachment posts, or struts, **18**. Posts **18** can be interconnected via a lower row **36***a* of circumferentially extending struts **20** and first and second rows upper rows **36***b*, **36***c*, respectively, of circumferentially extending struts **22** and **24**, respectively. The struts in each row desirably are arranged in a zig-zag or generally saw-tooth like pattern extending in the direction of the circumference of the frame as shown. Adjacent struts in the same row can be interconnected to one another as shown in FIGS. **1** and **5** to form an angle A, which desirably is between about 90 and 110 degrees, with about 100 degrees being a specific example. The selection of angle A between approximately 90 and 110 degrees optimizes the radial strength of frame **12** when expanded yet still permits the frame **12** to be evenly crimped and then expanded in the manner described below.

In the illustrated embodiment, pairs of adjacent circumferential struts in the same row are connected to each other by a respective, generally U-shaped crown structure, or crown portion, **26**. Crown structures **26** each include a horizontal portion extending between and connecting the adjacent ends of the struts such that a gap **28** is defined between the adjacent ends and the crown structure connects the adjacent ends at a location offset from the strut's natural point of intersection. Crown structures **26** significantly reduce residual strains on the frame **12** at the location of struts **20**, **22**, **24** during crimping and expanding of the frame **20** in the manner described below. Each pair of struts **22** connected at a common crown structure **26** forms a cell with an adjacent pair of struts **24** in the row above. Each cell can be connected to an adjacent cell at a node **32**. Each node **32** can be interconnected with the lower row of struts by a respective vertical (axial) strut **30** that is connected to and extends between a respective node **32** and a location on the lower row of struts **20** where two struts are connected at their ends opposite crown structures **26**.

In certain embodiments, lower struts **20** have a greater thickness or diameter than upper struts **22**, **24**. In one implementation, for example, lower struts **20** have a thickness T (FIG. **9**) of about 0.42 mm and upper struts **22**, **24** have a thickness T of about 0.38 mm. Because there is only one row of lower struts **20** and two rows of upper struts **22**, **24** in the illustrated configuration, enlargement of lower struts **20** with respect to upper struts **22**, **24** enhances the radial strength of the frame at the lower area of the frame and allows for more uniform expansion of the frame.

FIG. **9** shows a flattened view of a 120-degree segment of frame **12** shown in FIG. **7**, the segment comprising a portion of the frame extending between two posts **18**. As shown, the frame segment has three columns **34** and three rows **36***a*, **36***b*, **36***c* of struts per segment. Each column **34** is defined by the adjoining pairs of struts **20**, **22**, **24** extending between two axially extending struts **18**, **30**. Frame **12** desirably is comprised of three 120-degree segments, with each segment being bounded by two posts **18**. Accordingly, frame **12** in the illustrated embodiment includes 9 total columns per frame.

The number of columns and rows desirably is minimized to reduce the overall crimp profile of the valve, as further discussed below. The arrangement of FIGS. **7** and **9** typically is used for valves that are less than about 29 mm in diameter, and are most suitable for valves that are about 20-26 mm in diameter. In working examples of valves comprising frame **12**, a 20-mm valve can be crimped to a diameter of about 17 Fr, a 23-mm valve can be crimped to a diameter of about 18 Fr and a 26-mm valve can be crimped to a diameter of about 19 Fr. For valves that are about 29 mm and larger in diameter, it may be desirable to add another row and column of struts.

For example, FIGS. **8** and **10** show an alternative frame **40** that is similar to frame **12** except that frame **40** has four rows of struts (a lowermost, first row **52***a* of struts **42**, a second row **52***b* of struts **44**, a third row **52***c* of struts **46**, and an uppermost row **52***d* of struts **48**) instead of three rows of struts, as well as four columns **50** of struts for each 120-degree frame segment instead of three columns of struts. FIG. **10** shows a flattened view of a 120-degree segment of frame **40** shown in FIG. **8**. Frame **40** in the illustrated embodiment includes three such 120-degree segments, providing 12 total columns **50** of struts for the frame.

Struts **46** of the third row desirably are facing in the opposite direction of the struts **48** of the fourth row (i.e., the apexes or crown portions are facing in the opposite direction), to help avoid buckling of the vertical posts of the frame during crimping and expansion of the valve. Struts **44** of the second row can be arranged so as to be facing in the same direction as the struts **42** of the first row as shown (i.e., the apexes or crown portions are facing in the same direction). Alternatively, struts **44** of the second row can be facing in the opposing direction from struts **42** of the first row so as to form square cells, like the cells formed by the struts **46**, **48** of the third and fourth rows, respectively. Frame **40** can also include axially extending struts **54** connected to and extending between the ends of each strut **42**, **44**, **46**, and **48** aligned in a column **50** that are not connected to a post **18**. As noted above, frame **40** is most suitable for valves 29 mm and larger in diameter (when expanded to its functional size). In a working example of a valve incorporating frame **40**, a 29-mm valve can be crimped to a diameter of about 21 Fr.

Suitable plastically-expandable materials that can be used to form the frame include, without limitation, stainless steel, a nickel based alloy (e.g., a nickel-cobalt-chromium alloy), polymers, or combinations thereof. In particular embodiments, frame **20** is made of a nickel-cobalt-chromium-molybdenum alloy, such as MP35N™ (tradename of SPS Technologies), which is equivalent to UNS R30035 (covered by ASTM F562-02). MP35N™/UNS R30035 comprises 35% nickel, 35% cobalt, 20% chromium, and 10% molybdenum, by weight. It has been found that the use of MP35N to form frame **20** provides superior structural results over stainless steel. In particular, when MP35N is used as the frame material, less material is needed to achieve the same or better performance in radial and crush force resistance, fatigue resistances, and corrosion resistance. Moreover, since less material is required, the crimped profile of the frame can be reduced, thereby providing a lower profile valve assembly for percutaneous delivery to the treatment location in the body.

Referring again to FIG. **1**, skirt **16** can be formed, for example, of polyethylene terephthalate (PET) ribbon. The thickness of the skirt can vary, but is desirably less than 6 mil, and desirably less than 4 mil, and even more desirably about 2 mil. Skirt **16** can be secured to the inside of frame **12** via Lenzing sutures **56**, as shown in FIG. **1**. Leaflet structure **14** can be attached to the skirt via a thin PET

reinforcing strip **68** (or sleeve), discussed below, which enables a secure suturing and protects the pericardial tissue of the leaflet structure from tears. Leaflet structure **14** can be sandwiched between skirt **16** and the thin PET strip **68** as shown. Suture **58**, which secures the PET strip and the leaflet structure **14** to skirt **16** can be any suitable suture, such as an Ethibond suture. Suture **58** (shown forming in-and-out stitches in FIG. **5**) desirably tracks the curvature of the bottom edge of leaflet structure **14**, as described in more detail below. Leaflet structure **14** can be formed of bovine pericardial tissue, biocompatible synthetic materials, or various other suitable natural or synthetic materials as known in the art and described in U.S. Pat. No. 6,730,118, which is incorporated by reference herein.

Leaflet structure **14** can comprise three leaflets **60**, which can be arranged to collapse in a tricuspid arrangement, as best shown in FIGS. **2** and **6**. The lower edge of leaflet structure **14** desirably has an undulating, curved scalloped shape (suture line **58** shown in FIG. **1** tracks the scalloped shape of the leaflet structure). By forming the leaflets with this scalloped geometry, stresses on the leaflets are reduced, which in turn improves durability of the valve. Moreover, by virtue of the scalloped shape, folds and ripples at the belly of each leaflet (the central region of each leaflet), which can cause early calcification in those areas, can be eliminated or at least minimized. The scalloped geometry also reduces the amount of tissue material used to form leaflet structure, thereby allowing a smaller, more even crimped profile at the inflow end of the valve.

Leaflets **60** can be secured to one another at their adjacent sides to form commissures **84** of the leaflet structure (the edges where the leaflets come together). Leaflet structure **14** can be secured to frame **12** using suitable techniques and mechanisms. For example, as best shown in FIG. **6**, commissures **84** of the leaflet structure desirably are aligned with the support posts **18** and secured thereto using sutures. The point of attachment of the leaflets to the posts **18** can be reinforced with bars **62** (FIG. **11**), which desirably are made of a relatively rigid material (compared to the leaflets), such as stainless steel.

FIG. **13** shows a single leaflet **60**, which has a curved lower edge **64** and two flaps **66** extending between the upper edge and curved lower edge of the leaflet. The curved lower edge **64** forms a single scallop. When secured to two other leaflets to form leaflet structure **14**, the curved lower edges of the leaflets collectively form the scalloped shaped lower edge portion of the leaflet structure (as best shown in FIG. **18**). As further shown in FIG. **13**, two reinforcing bars **62** can be secured to the leaflet adjacent to flaps **66** (e.g., using sutures). The flaps can then be folded over bars **62** and secured in the folded position using sutures. If desired, as shown in FIG. **12**, each bar **62** can be placed in a protective sleeve **68** (e.g., a PET sleeve) before being secured to a leaflet.

As shown in FIG. **14**, the lower curved edge **64** of the leaflet can be reinforced for later securement to the skirt **16**, such as by securing a reinforcing strip **68** along the curved lower edge between flaps **66** on the side of the leaflet opposite bars **62**. Three such leaflets **60** can be prepared in the same manner and then connected to each other at their flaps **66** in a tricuspid arrangement to form leaflet structure **14**, as shown in FIG. **15**. The reinforcing strips **68** on the leaflets collectively define a ribbon or sleeve that extends along the lower edge portion of the inside surface of the leaflet structure.

As noted above, leaflet structure **14** can be secured to frame **12** with skirt **16**. Skirt **16** desirably comprises a tough, tear resistant material such as PET, although various other synthetic or natural materials can be used. Skirt **16** can be much thinner than traditional skirts. In one embodiment, for example, skirt **16** is a PET skirt having a thickness of about 0.07 mm at its edges and about 0.06 mm at its center. The thinner skirt can provide for better crimping performances while still providing good perivalvular sealing.

FIG. **16** shows a flattened view of the skirt before the opposite ends are secured to each other to form the annular shape shown in FIG. **17**. As shown, the upper edge of skirt **16** desirably has an undulated shape that generally follows the shape of the second row of struts **22** of the frame. In this manner, the upper edge of skirt **16** can be tightly secured to struts **22** with sutures **56** (as best shown in FIG. **1**). Skirt **16** can also be formed with slits **70** to facilitate attachment of the skirt to the frame. Slits **70** are aligned with crown structures **26** of struts **22** when the skirt is secured to the frame. Slits **70** are dimensioned so as to allow an upper edge portion of skirt to be partially wrapped around struts **22** and reduce stresses in the skirt during the attachment procedure. For example, in the illustrated embodiment, skirt **16** is placed on the inside of frame **12** and an upper edge portion of the skirt is wrapped around the upper surfaces of struts **22** and secured in place with sutures **56**. Wrapping the upper edge portion of the skirt around struts **22** in this manner provides for a stronger and more durable attachment of the skirt to the frame. Although not shown, the lower edge of the skirt can be shaped to conform generally to the contour of the lowermost row of struts **22** to improve the flow of blood past the inflow end of the valve.

As further shown in FIG. **17**, various suture lines can be added to the skirt to facilitate attachment of the skirt to the leaflet structure and to the frame. For example, a scalloped shaped suture line **72** can be used as a guide to suture the lower edge of the leaflet structure at the proper location against the inner surface of the skirt using suture **59** (as best shown in FIG. **5**). Another scalloped shaped suture line **74** (FIG. **17**) can be use as a guide to suture the leaflet structure to the skirt using sutures **58** (FIG. **1**). Reinforcing strips **68** secured to the lower edge of the leaflets reinforces the leaflets along suture line **58** and protects against tearing of the leaflets. FIG. **18** shows a leaflet assembly comprised of skirt **16** and leaflet structure **14** secured to the skirt. The leaflet assembly can then be secured to frame **12** in the manner described below. In alternative embodiments, the skirt, without the leaflet structure, can be connected to the frame first, and then the leaflet structure can be connected to the skirt.

FIG. **6** shows a top view of the valve assembly attached to frame **12**. Leaflets **60** are shown in a generally closed position. As shown, the commissures of the leaflets are aligned with posts **18** of the frame. The leaflets can be secured to the frame using sutures extending through flaps **66** of the leaflets, openings **76** in bars **62**, and openings **78** in posts **18**, effectively securing flaps **66** to posts **18**. As noted above, bars **62** reinforce the flaps at the area of connection with posts and protect against tearing of the leaflets.

As shown in FIG. **6A**, bars **62** desirably are aligned perpendicular and as straight as possible with respect to posts **18** of the frame, such that bars **62** and post **18** at each commissure form a "T" shape. The width of bars **62** and the attachment of the commissures via the bars provides a clearance between the deflectable portions of the leaflets **60** (the portions not secured by sutures to the frame) and the frame, while the edge radius (thickness) of bars **62** serves as a flex hinge for the leaflets **60** during valve opening and

closing, thereby increasing the space between the leaflets and the frame. By increasing the space between the moving portions of the leaflets and frame and by having the leaflets flex against an edge radius of bars **62**, contact between the moving portions of the leaflets (especially the outflow edges of the leaflets) and the frame can be avoided during working cycles, which in turn improves the durability of the valve assembly. This configuration also enhances perfusion through the coronary sinuses.

FIG. **19** depicts a side view of a valve **10** crimped on a balloon delivery catheter **100**. The valve is crimped onto balloon **110** of balloon catheter **100**. It is desirable to protect leaflet structure **14** of the valve from damage during crimping to ensure durability of the leaflet structure and at the same time, it is desirable to reduce as much as possible the crimped profile size of the valve. During the crimping procedure the tissue of the leaflet structure (e.g., bovine pericardial tissue or other suitable tissue) is pressed against against the inner surface of the metal frame and portions of the tissue can protrude into the open cells of the frame between the struts and can be pinched due to the scissor-like motion of the struts of the frame. If the valve is severely crimped to achieve a small crimping size, this scissor-like motion can result in cuts and rupture of the tissue leaflets.

Skirt **16**, described above, can protect against damage to the leaflet structure during crimping to a certain degree. However, the skirt's main purpose is structural and it does not in certain embodiments cover the entire frame. Therefore, in such embodiments, the skirt may not fully protect the leaflet structure during crimping and as such, the frame can still cause damage to the leaflet structure.

FIGS. **20** and **21** show an embodiment of a crimping apparatus for atraumatic crimping of a valve onto a balloon in a manner that further protects against damage to the leaflets. The crimping apparatus (also referred to as a crimper), indicated generally at **200**, has an aperture **202** sized to receive a valve in an expanded state. FIG. **20** shows aperture **202** in a fully open or dilated state with a valve **10** positioned inside aperture **202**. Crimping apparatus **200** has a plurality of crimper jaws **206** (12 in the illustrated embodiment) which are configured to move radially inwardly to radially compress (crimp) the valve to a smaller profile around the balloon of a balloon catheter.

A deformable material is positioned between the outside of the frame and the crimping jaws **206**. In the illustrated embodiment, the deformable material comprises a protective sleeve, or covering, **204** that is placed around the valve so that it covers the outer surface of the frame of the valve and prevents the hard surface of the crimping jaws from directly contacting the frame of the valve. The sleeve **204** desirably is sized to fully cover the outer surface of the frame. Sleeve **204** desirably is made of a soft, flexible and compressible material. The sleeve can be formed from generally available materials, including, but not limited to, natural or synthetic sponge (e.g., polyurethane sponge), a foamed material made of a suitable polymer such as polyurethane or polyethylene, or any of various suitable elastomeric materials, such as polyurethane, silicon, polyolefins or a variety of hydrogels, to name a few.

The sleeve is desirably stored in a wet environment (e.g., immersed in saline) prior to use. After placing sleeve **204** around the valve, the valve and the sleeve are placed into crimping apparatus **200** as shown in FIG. **20**. Balloon **110** of a balloon catheter can then be positioned within the leaflets **60** of the valve (FIG. **21**). FIG. **21** shows crimper jaws **206** surrounding sleeve **204**, which in turn surrounds frame **12** and leaflet structure **14** of valve **10**. Balloon **110** typically is placed at the center of the valve so that the valve can be evenly expanded during implantation of the valve within the body.

As seen in FIG. **21**, during crimping, the sponge-like material of protective sleeve **204** protrudes into the open cells of frame **12** and occupies this space, thereby preventing leaflet structure **14** from entering this space and being pinched or otherwise damaged. After crimping is completed, the valve with the protective sleeve is removed from the crimping apparatus. Sleeve **204** can then be gently peeled away from the frame. Because the protective sleeve presses the leaflet structure inwardly and away from the frame during crimping, the valve can be crimped to a small profile without damaging the leaflet structure.

FIGS. **23** and **24** illustrate an advantage that can be gained by using protective sleeve **204**. FIG. **23** shows a prosthetic valve that was crimped without using the protective sleeve. Dotted line **300** identifies an area of the valve where leaflet structure **302** has been pressed between struts of a frame **304**, which can damage the leaflet structure as discussed above.

In contrast, FIG. **24** shows a prosthetic valve that was crimped using protective sleeve **204**. In this example, leaflet structure **302** was pressed inwardly and away from the inside of frame **304** and, therefore, the leaflet structure was not pinched or squeezed between the struts of the frame.

Accordingly, since the leaflet structure is pushed away from the frame when the protective sleeve is used, the leaflet structure is less likely to be pinched or cut during the crimping process. Also, when using a protective sleeve, a very ordered structure of balloon-leaflets-frame (from inward to outward) can be achieved. When no such protective sleeve is utilized, some portion of the balloon, leaflets, and frame are much more likely to overlap after the crimping procedure and the resulting structure is less predictable and uniform.

In addition to the foam or sponge-type protective sleeve described above, other types of sleeves or protective layers of deformable material can be used to protect the leaflets against damage during crimping of a valve. In one implementation, for example, a layer (e.g., rectangular slices) of deformable material (e.g., sponge, rubber, silicon, polyurethane, etc.) can be disposed on each crimping jaw **206** so as to form a sleeve around the valve upon crimping. Alternatively, deformable packets filled with a flowable, deformable material, such as a gel or gas, can be disposed on each crimping jaw for contacting the valve upon crimping. In addition, the deformable material (e.g., sleeve **204**) can be covered with a thin PET cloth, among many other fabric materials or other suitable materials, to prevent particles of the deformable materials from migrating to the valve during crimping.

The skirt of a prosthetic valve serves several functions. In particular embodiments, for example, the skirt functions to seal and prevent (or decrease) perivalvular leakage, to anchor the leaflet structure to the frame, and to protect the leaflets against damage caused by contact with the frame during crimping and during working cycles of the valve. The skirt used with the prosthetic valve discussed above has been described as being a fabric, such as a PET cloth. PET or other fabrics are substantially non-elastic (i.e., substantially non-stretchable and non-compressible). As such, the skirt in certain implementations limits the smallest achievable crimping diameter of the valve and can wrinkle after expansion from the crimped diameter.

In alternative embodiments, such as discussed below, a prosthetic valve can be provided with a skirt that is made of

a stretchable and/or compressible material, such as silicon. Due to the compressibility of such a skirt, the valve can be crimped to a relatively smaller diameter as compared to a valve having a non-compressible skirt. Furthermore, such a skirt can recover its original, smooth surfaces with little or no wrinkling after expansion from the crimped state.

FIG. **25** shows an embodiment of a frame **12** that has an elastic "over-tube" skirt or sleeve **340** that extends completely around and covers at least a portion of the outside of the frame. In particular embodiments, skirt **340** is made of silicon, which can undergo large deformations while maintaining its elasticity. Such a silicon skirt can be a thin sleeve that covers a portion of frame **12** from the outside. In the illustrated embodiment, the height of the skirt is less than the overall height of frame **12**, however, the skirt can vary in height and need not be the height shown in FIG. **25**. For example, the height of the skirt can be the same as or greater than that of the frame so as to completely cover the outside of the frame. In an alternative embodiment, the skirt **340** can be mounted to the inside of the frame using, for example, sutures or an adhesive. When mounted inside of the frame, the skirt can protect the leaflets from abrasion against the inside of the frame. Other materials that can be used to form the skirt or sleeve include, but are not limited to, PTFE, ePTFE, polyurethane, polyolefins, hydrogels, biological materials (e.g., pericardium or biological polymers such as collagen, gelatin, or hyaluronic acid derivatives) or combinations thereof.

In another embodiment, the entire frame or a portion thereof can be dipped in liquefied material (e.g., liquid silicon or any of the materials described above for forming the sleeve **340** that can be liquefied for dip coating the frame) in order to encapsulate the entire frame (or at least that portion that is dipped) in silicon. FIG. **26** is a side view of a frame **12** that has been dipped in silicon to form a continuous cylindrical silicon covering **342** encapsulating the struts of the frame and filling the spaces between the struts. FIG. **26** shows the covering **342** before it is trimmed to remove excess material extending beyond the ends of the frame. Although less desirable, the frame can be dipped such that the silicon encapsulates the struts of the frame but does not fill the open spaces between the struts of the frame.

FIG. **27** shows an embodiment of a prosthetic valve **400** comprising a frame **402** and a leaflet structure **404** mounted to the inside of the frame (e.g., using sutures as shown). Frame **402** has a skirt in the form of silicon covering **406** that is formed, for example, by dipping the frame into liquid silicon. FIG. **27** shows valve **400** in its expanded state. In FIG. **28**, valve **400** has been crimped to a smaller profile. During crimping, coating **406**, which extends across and fills the open cells between the struts of the frame, is effective to push leaflet structure **404** inward and away from the frame, thereby protecting the leaflet structure from pinching or tearing. FIG. **29** shows valve **400** after being expanded by a balloon of a balloon catheter.

In order to test the durability and stretch resistance of the silicon used, several uniaxial tests were conducted. In particular, silicon strips of about 5×50 mm (with a thickness of about 0.85 mm) were tested in a uniaxial tester. FIGS. **30**A-**30**C show graphs of the results of the uniaxial testing of silicon strips. In addition, tears were deliberately introduced into silicon strips at a middle of the strips and at the edge of the strips while the strips were stretched on a uniaxial tester. The tears were introduced by making holes in the silicon strips with a needle. FIGS. **31**A-**31**F show graphs of the results of the uniaxial testing of silicon strips with deliberately introduced tears.

It was found that ultimate tensile stretch for a thin layer of silicon was over 500% and that samples that had tears that were deliberately introduced continued to show notable strength. Accordingly, the elasticity of silicon permits silicon dipped frames to be crimped to very low profiles and expanded back out to larger profiles without significant damage to the silicon layer. In addition, the silicon material can increase friction between the frame and the native annulus where the prosthetic valve is implanted, resulting in better anchoring and preventing/reducing perivalvular leaks.

A silicon skirt can be mounted on a frame by various means, including by using a mandrel. Also, it may be desirable to use a silicon skirt in combination with a cloth or fabric skirt. For example, it may be desirable to place a silicon skirt on the outside of a cloth or fabric skirt that is surrounding at least a portion of a frame.

Alternatively or additionally, a silicon skirt could also be placed on the inside of the frame and attached to the frame so that it offers the leaflets improved protecting during working cycles. Alternatively, instead of silicon, the skirt can be made of an auxetic and/or swelling material, such as synthetic or natural hydrogels. An auxetic material is one that expands laterally while stretched longitudinally, which means that this material has a negative Poisson ration. If the frame is covered with an auxetic material it can expand radially while being stretched circumferentially when the valve is expanded from its crimped state. Such expansion can improve the fit of the valve at the native valve annulus, thereby preventing or reducing perivalvular leakage.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope and spirit of these claims.

We claim:

1. A method of assembling an implantable prosthetic valve, comprising:

suturing a reinforcing member to an inner surface of a leaflet structure adjacent a lower edge of the leaflet structure;

suturing a skirt member to an outer surface of the leaflet structure along a scallop line that tracks the lower edge of the leaflet structure to form an assembly comprised of the skirt member, the leaflet structure, and the reinforcing member;

placing the assembly inside of a radially collapsible and expandable annular frame, wherein the frame comprises a plastically deformable material selected from the group comprising stainless steel and a nickel-cobalt based alloy; and

suturing the skirt member to struts of the frame;

wherein the leaflet structure comprises three leaflets, each having a curved lower edge and the act of suturing the reinforcing member comprises suturing the reinforcing member to inner surfaces of the leaflets adjacent their curved lower edges.

2. The method of claim **1**, wherein the reinforcing member comprises three separate reinforcing members, each of which is sutured to an inner surface of a respective leaflet adjacent its curved lower edge.

3. The method of claim **1**, further comprising securing commissures of the leaflet structure to respective commissure attachment portions of the frame.

4. The method of claim 1, wherein the leaflets comprises pericardium and each of the reinforcing member and the skirt member comprises a fabric.

5. The method of claim 1, wherein the reinforcing member and the skirt member are separate pieces of material and the reinforcing member is sutured to the leaflet structure prior to suturing the skirt member to the leaflet structure.

6. A method of assembling an implantable prosthetic valve, comprising:

suturing a reinforcing member to an inner surface of a leaflet structure adjacent a lower edge of the leaflet structure;

suturing a skirt member to an outer surface of the leaflet structure along a scallop line that tracks the lower edge of the leaflet structure to form an assembly comprised of the skirt member, the leaflet structure, and the reinforcing member;

placing the assembly inside of a radially collapsible and expandable annular frame, wherein the frame comprises a plastically deformable material selected from the group comprising stainless steel and a nickel-cobalt based alloy; and

suturing the skirt member to struts of the frame;

wherein the lower edge of the leaflet structure is secured to the frame only indirectly by the skirt member.

7. A method of assembling an implantable prosthetic valve, comprising:

suturing a reinforcing member to an inner surface of a leaflet structure adjacent a lower edge of the leaflet structure;

suturing a skirt member to an outer surface of the leaflet structure along a scallop line that tracks the lower edge of the leaflet structure to form an assembly comprised of the skirt member, the leaflet structure, and the reinforcing member;

placing the assembly inside of a radially collapsible and expandable annular frame, wherein the frame comprises a plastically deformable material selected from the group comprising stainless steel and a nickel-cobalt based alloy; and

suturing the skirt member to struts of the frame;

wherein the lower edge of the leaflet structure is sutured only to the skirt member and the reinforcing member.

8. A method of assembling an implantable prosthetic valve, comprising:

suturing a reinforcing member to inner surfaces of three tissue leaflets adjacent curved lower edges of the leaflets;

suturing a skirt member to outer surfaces of the leaflets with a suture that extends through the skirt member, the leaflets, and the reinforcing member along a scallop line that tracks the curved lower edges of the leaflets to form an assembly comprised of the skirt member, the leaflets, and the reinforcing member;

placing the assembly inside of a radially collapsible and expandable annular frame, the annular frame comprising at least three rows of circumferentially extending rows of angled struts including a first row of angled struts defining an inflow end of the frame, a second row of angled struts defining an outflow end of the frame, and a third row of angled struts positioned axially between the first and second rows of angled struts along a length of the frame, wherein the frame comprises a plastically deformable material selected from the group comprising stainless steel and a nickel-cobalt based alloy; and

suturing the skirt member to struts of the first and third rows of angled struts.

9. The method of claim 8, wherein the act of suturing the skirt member to the outer surfaces of the leaflets comprises forming in-and-out stitches with an Ethibond suture that extends through the skirt member, the leaflets, and the reinforcing member along the scallop line.

10. The method of claim 8, wherein each leaflet has two side flaps, wherein each side flap is connected to an adjacent side flap of another leaflet to form commissures of the leaflet structure, and the method further comprises securing the commissures of the leaflets to commissure attachment portions of the frame.

11. The method of claim 1, wherein the reinforcing member comprises three separate reinforcing members, each of which is sutured to an inner surface of a respective leaflet adjacent its curved lower edge.

12. The method of claim 8, wherein the act of the suturing the skirt member to struts of the first and third rows of angled struts comprises suturing a lower edge portion of the skirt member to struts of the first row of angled struts and suturing an upper edge portion of the skirt member to struts of the second row of angled struts.

13. The method of claim 12, wherein the second and third rows of angled struts define upper and lower boundaries of an upper row of closed cells of the frame defining openings in the frame, and wherein the skirt member covers the entire extent of an inner surface of the frame except for the openings in the upper row of cells.

14. The method of claim 12, wherein suturing the upper edge portion of the skirt member to struts of the second row of angled struts comprises partially wrapping the upper edge portion of the skirt member around the struts of the second row of angled struts.

15. The method of claim 12, wherein the struts of the third row of angled struts are arranged in a zig-zag pattern and the upper edge portion of the skirt member comprises a zig-zag pattern that generally conforms to the zig-zag pattern of the third row of angled struts.

16. The method of claim 12, wherein the lower edges of the leaflets are secured to the frame only indirectly by the skirt member.

17. A method of assembling an implantable prosthetic valve, comprising:

placing a reinforcing member along a first surface of a leaflet structure adjacent an undulating lower edge of the leaflet structure;

placing a skirt member along a second surface of the leaflet structure;

securing the skirt member to the leaflet structure by forming in-and-out stitches with a suture that extends through the skirt member, the leaflet structure, and the reinforcing member along a scallop line that tracks the lower edge of the leaflet structure to form an assembly comprised of the skirt member, the leaflet structure, and the reinforcing member;

subsequent to securing the skirt member to the leaflet structure to form the assembly, placing the assembly inside of a radially collapsible and expandable annular frame, wherein the frame comprises a plastically deformable material selected from the group comprising stainless steel and a nickel-cobalt based alloy; and

suturing the skirt member to struts of the frame;

wherein the reinforcing member and the skirt member are separate pieces of material and the reinforcing member

is sutured to the leaflets prior to securing the skirt member to the leaflet structure with the in-and-out stitches.

18. The method of claim **17**, wherein the plastically deformable material comprises a nickel-cobalt-chromium-molybdenum alloy.

* * * * *

US009393110B2

(12) **United States Patent**
Levi et al.

(10) **Patent No.: US 9,393,110 B2**
(45) **Date of Patent: Jul. 19, 2016**

(54) **PROSTHETIC HEART VALVE**

(75) Inventors: **Tamir S. Levi**, Moshav Ein HaEmek (IL); **Son V. Nguyen**, Irvine, CA (US); **Netanel Benichou**, D.N. Hof HaCarmel (IL); **David Maimon**, Haifa (IL); **Ziv Yohanan**, Yesud Hamaala (IL); **Nikolay Gurovich**, Hadera (IL); **Bella Felsen**, Haifa (IL); **Larisa Dadonkina**, Or Akiva (IL); **Ron Sharoni**, Hadera (IL); **Elena Sherman**, Ramat Hasharon (IL)

(73) Assignee: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 844 days.

(21) Appl. No.: **13/253,689**

(22) Filed: **Oct. 5, 2011**

(65) **Prior Publication Data**

US 2012/0123529 A1 May 17, 2012

Related U.S. Application Data

(60) Provisional application No. 61/390,107, filed on Oct. 5, 2010, provisional application No. 61/508,513, filed on Jul. 15, 2011.

(51) **Int. Cl.**
A61F 2/24 (2006.01)

(52) **U.S. Cl.**
CPC ..... ***A61F 2/2412*** (2013.01); ***A61F 2/2418*** (2013.01); ***A61F 2/2433*** (2013.01); (Continued)

(58) **Field of Classification Search**
CPC A61F 2/24; A61F 2/2412; A61F 2/2418; A61F 2/2427; A61F 2/243; A61F 2/2433; A61F 2/2469; A61F 2220/0075; A61F 2250/0036; A61F 2250/0039
USPC 623/2.11, 2.12, 2.17, 2.19, 1.11, 1.12, 623/1.24, 1.26
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,409,013 A 11/1968 Berry
3,467,102 A 9/1969 Fogarty et al.

(Continued)

FOREIGN PATENT DOCUMENTS

DE 2246526 A1 3/1973
DE 19532846 A1 3/1997

(Continued)

OTHER PUBLICATIONS

International Search Report from corresponding PCT application No. PCT/US2011/054973 dated Apr. 23, 2012.

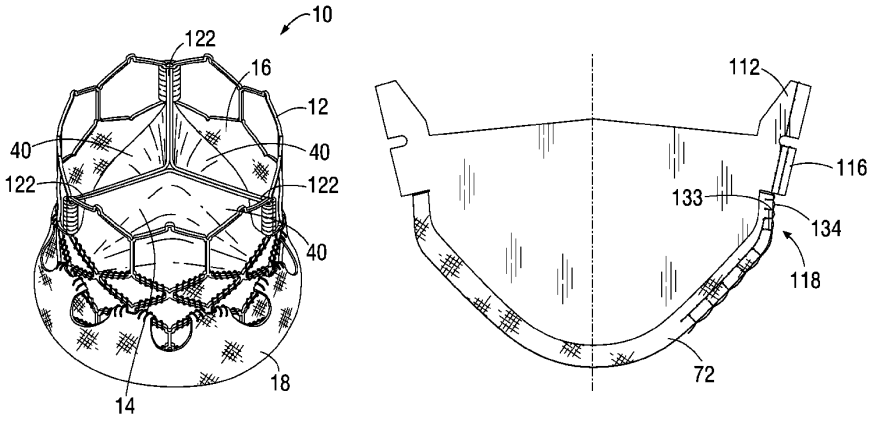
(Continued)

Primary Examiner — Todd J Scherbel
(74) *Attorney, Agent, or Firm* — Klarquist Sparkman LLP; David L. Hauser; AnneMarie Kaiser

(57) **ABSTRACT**

Embodiments of a radially collapsible and expandable prosthetic heart valve are disclosed. A valve frame can have a tapered profile when mounted on a delivery shaft, with an inflow end portion having a smaller diameter than an outflow end portion. The valve can comprise generally V-shaped leaflets, reducing material within the inflow end of the frame. An outer skirt can be secured to the outside of the inflow end portion of the frame, the outer skirt having longitudinal slack when the valve is expanded and lying flat against the frame when the valve is collapsed. A diagonally woven inner skirt can elongate axially with the frame. Side tabs of adjacent leaflets can extend through and be secured to window frame portions of the frame to form commissures. The window frame portions can be depressed radially inward relative to surrounding frame portions when the valve is crimped onto a delivery shaft.

25 Claims, 26 Drawing Sheets



(52) **U.S. Cl.**
CPC . *A61F2220/0075* (2013.01); *A61F 2230/0054* (2013.01); *A61F 2250/0036* (2013.01); *A61F 2250/0097* (2013.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,548,417	A	12/1970	Kisher
3,587,115	A	6/1971	Shiley
3,657,744	A	4/1972	Ersek
3,671,979	A	6/1972	Moulopoulos
3,714,671	A	2/1973	Edwards et al.
3,755,823	A	9/1973	Hancock
3,983,581	A	10/1976	Angell et al.
4,035,849	A	7/1977	Angell et al.
4,056,854	A	11/1977	Boretos et al.
4,106,129	A	8/1978	Carpentier et al.
4,222,126	A	9/1980	Boretos et al.
4,265,694	A	5/1981	Boretos et al.
4,297,749	A	11/1981	Davis et al.
4,339,831	A	7/1982	Johnson
4,343,048	A	8/1982	Ross et al.
4,345,340	A	8/1982	Rosen
4,373,216	A	2/1983	Klawitter
4,406,022	A	9/1983	Roy
4,470,157	A	9/1984	Love
4,535,483	A	8/1985	Klawitter et al.
4,574,803	A	3/1986	Storz
4,592,340	A	6/1986	Boyles
4,605,407	A	8/1986	Black et al.
4,612,011	A	9/1986	Kautzky
4,643,732	A	2/1987	Pietsch et al.
4,655,771	A	4/1987	Wallsten
4,692,164	A	9/1987	Dzemeshkevich et al.
4,733,665	A	3/1988	Palmaz
4,759,758	A	7/1988	Gabbay
4,762,128	A	8/1988	Rosenbluth
4,777,951	A	10/1988	Cribier et al.
4,787,899	A	11/1988	Lazarus
4,796,629	A	1/1989	Grayzel
4,797,901	A	1/1989	Goerne et al.
4,829,990	A	5/1989	Thuroff et al.
4,851,001	A	7/1989	Taheri
4,856,516	A	8/1989	Hillstead
4,878,495	A	11/1989	Grayzel
4,878,906	A	11/1989	Lindemann et al.
4,883,458	A	11/1989	Shiber
4,922,905	A	5/1990	Strecker
4,966,604	A	10/1990	Reiss
4,979,939	A	12/1990	Shiber
4,986,830	A	1/1991	Owens et al.
4,994,077	A	2/1991	Dobben
5,007,896	A	4/1991	Shiber
5,026,366	A	6/1991	Leckrone
5,032,128	A	7/1991	Alonso
5,037,434	A	8/1991	Lane
5,047,041	A	9/1991	Samuels
5,059,177	A	10/1991	Towne et al.
5,080,668	A	1/1992	Bolz et al.
5,085,635	A	2/1992	Cragg
5,089,015	A	2/1992	Ross
5,152,771	A	10/1992	Sabbaghian et al.
5,163,953	A	11/1992	Vince
5,167,628	A	12/1992	Boyles
5,192,297	A	3/1993	Hull
5,258,023	A	11/1993	Reger
5,266,073	A	11/1993	Wall
5,282,847	A	2/1994	Trescony et al.
5,295,958	A	3/1994	Shturman
5,332,402	A	7/1994	Teitelbaum
5,360,444	A	11/1994	Kusuhara
5,370,685	A	12/1994	Stevens
5,397,351	A	3/1995	Pavcnik et al.
5,411,055	A	5/1995	Kane
5,411,552	A	5/1995	Andersen et al.
5,443,446	A	8/1995	Shturman
5,480,424	A	1/1996	Cox
5,500,014	A	3/1996	Quijano et al.
5,545,209	A	8/1996	Roberts et al.
5,545,214	A	8/1996	Stevens
5,549,665	A	8/1996	Vesely et al.
5,554,185	A	9/1996	Block et al.
5,571,175	A	11/1996	Vanney et al.
5,591,185	A	1/1997	Kilmer et al.
5,607,464	A	3/1997	Trescony et al.
5,609,626	A	3/1997	Quijano et al.
5,628,786	A	5/1997	Banas et al.
5,639,274	A	6/1997	Fischell et al.
5,665,115	A	9/1997	Cragg
5,716,417	A	2/1998	Girard et al.
5,728,068	A	3/1998	Leone et al.
5,749,890	A	5/1998	Shaknovich
5,756,476	A	5/1998	Epstein et al.
5,769,812	A	6/1998	Stevens et al.
5,776,188	A	7/1998	Shepherd et al.
5,800,508	A	9/1998	Goicoechea et al.
5,840,081	A	11/1998	Andersen et al.
5,843,161	A	12/1998	Solovay
5,855,597	A	1/1999	Jayaraman
5,855,601	A	1/1999	Bessler et al.
5,855,602	A	1/1999	Angell
5,925,063	A	7/1999	Khosravi
5,928,281	A	7/1999	Huynh et al.
5,957,949	A	9/1999	Leonhardt et al.
6,027,525	A	2/2000	Suh et al.
6,110,198	A	8/2000	Fogarty et al.
6,132,473	A	10/2000	Williams et al.
6,168,614	B1	1/2001	Andersen et al.
6,171,335	B1	1/2001	Wheatley et al.
6,174,327	B1	1/2001	Mertens et al.
6,210,408	B1	4/2001	Chandrasekaran et al.
6,217,585	B1	4/2001	Houser et al.
6,221,091	B1	4/2001	Khosravi
6,231,602	B1	5/2001	Carpentier et al.
6,245,102	B1	6/2001	Jayaraman
6,299,637	B1	10/2001	Shaolian et al.
6,302,906	B1	10/2001	Goicoechea et al.
6,306,164	B1	10/2001	Kujawski
6,312,465	B1	11/2001	Griffin et al.
6,350,277	B1	2/2002	Kocur
6,352,554	B2	3/2002	De Paulis
6,425,916	B1	7/2002	Garrison et al.
6,440,164	B1	8/2002	DiMatteo et al.
6,454,799	B1	9/2002	Schreck
6,458,153	B1	10/2002	Bailey et al.
6,461,382	B1	10/2002	Cao
6,468,660	B2	10/2002	Ogle et al.
6,482,228	B1	11/2002	Norred
6,488,704	B1	12/2002	Connelly et al.
6,569,196	B1	5/2003	Vesely
6,605,112	B1	8/2003	Moll et al.
6,610,088	B1	8/2003	Gabbay
6,729,356	B1	5/2004	Baker et al.
6,730,118	B2	5/2004	Spenser et al.
6,733,525	B2	5/2004	Yang et al.
6,767,362	B2	7/2004	Schreck
6,814,754	B2	11/2004	Greenhalgh
6,830,584	B1	12/2004	Seguin
6,837,902	B2	1/2005	Nguyen
6,893,460	B2	5/2005	Spenser et al.
6,908,481	B2	6/2005	Cribier
6,911,040	B2	6/2005	Johnson et al.
7,018,406	B2	3/2006	Seguin et al.
7,101,396	B2	9/2006	Artof
7,147,663	B1	12/2006	Berg et al.
7,261,732	B2	8/2007	Justino
7,264,632	B2	9/2007	Wright et al.
7,267,686	B2	9/2007	Dimatteo et al.
7,276,078	B2	10/2007	Spenser et al.
7,276,084	B2	10/2007	Yang et al.
7,374,571	B2	5/2008	Pease et al.
7,393,360	B2	7/2008	Spenser et al.
7,399,315	B2	7/2008	Iobbi
7,462,191	B2	12/2008	Spenser et al.
7,481,838	B2	1/2009	Carpentier et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,510,575	B2	3/2009	Spenser et al.	
7,524,331	B2	4/2009	Birdsall	
7,597,711	B2	10/2009	Drews et al.	
7,780,725	B2	8/2010	Haug et al.	
7,871,435	B2	1/2011	Carpentier et al.	
7,914,569	B2	3/2011	Nguyen et al.	
7,951,197	B2	5/2011	Lane et al.	
7,959,674	B2	6/2011	Shu et al.	
7,967,857	B2	6/2011	Lane	
7,972,378	B2	7/2011	Tabor et al.	
8,083,793	B2	12/2011	Lane et al.	
8,226,710	B2	7/2012	Nguyen et al.	
8,348,995	B2	1/2013	Tuval et al.	
8,348,998	B2 *	1/2013	Pintor et al.	623/2.11
8,349,000	B2	1/2013	Schreck	
8,425,593	B2	4/2013	Braido et al.	
8,454,685	B2	6/2013	Hariton et al.	
8,512,396	B2	8/2013	Styrc	
8,673,000	B2	3/2014	Tabor et al.	
8,747,460	B2	6/2014	Tuval et al.	
8,771,345	B2	7/2014	Tuval et al.	
8,808,356	B2	8/2014	Braido et al.	
8,845,721	B2	9/2014	Braido et al.	
8,992,608	B2	3/2015	Haug et al.	
2001/0021872	A1	9/2001	Bailey et al.	
2001/0027338	A1	10/2001	Greenberg	
2002/0032481	A1	3/2002	Gabbay	
2002/0173842	A1	11/2002	Buchanan	
2003/0050694	A1	3/2003	Yang et al.	
2003/0100939	A1	5/2003	Yodfat et al.	
2003/0114913	A1	6/2003	Spenser et al.	
2003/0212454	A1	11/2003	Scott et al.	
2003/0236568	A1	12/2003	Hojeibane et al.	
2004/0039436	A1 *	2/2004	Spenser et al.	623/1.13
2004/0186565	A1	9/2004	Schreck	
2004/0260389	A1	12/2004	Case et al.	
2005/0075718	A1	4/2005	Nguyen et al.	
2005/0075725	A1	4/2005	Rowe	
2005/0234546	A1	10/2005	Nugent et al.	
2006/0025857	A1	2/2006	Bergheim et al.	
2006/0149350	A1	7/2006	Patel et al.	
2006/0178740	A1	8/2006	Stacchino et al.	
2006/0195186	A1	8/2006	Drews et al.	
2006/0229719	A1	10/2006	Marquez et al.	
2006/0259136	A1 *	11/2006	Nguyen et al.	623/2.18
2006/0259137	A1	11/2006	Artof et al.	
2006/0265056	A1	11/2006	Nguyen et al.	
2007/0073387	A1	3/2007	Forster	
2007/0270944	A1	11/2007	Bergheim et al.	
2008/0021546	A1	1/2008	Patz et al.	
2008/0154355	A1	6/2008	Benichou et al.	
2008/0208327	A1	8/2008	Rowe	
2008/0243245	A1	10/2008	Thambar et al.	
2008/0243246	A1	10/2008	Ryan et al.	
2009/0264997	A1	10/2009	Salahieh et al.	
2009/0287296	A1	11/2009	Manasse	
2009/0287299	A1 *	11/2009	Tabor et al.	623/1.26
2010/0082094	A1 *	4/2010	Quadri et al.	623/1.26
2010/0100176	A1	4/2010	Elizondo et al.	
2010/0168839	A1	7/2010	Braido et al.	
2010/0185277	A1 *	7/2010	Braido et al.	623/2.18
2010/0204781	A1	8/2010	Alkhatib	
2010/0262231	A1	10/2010	Tuval et al.	
2011/0022157	A1 *	1/2011	Essinger	A61F 2/2418 623/1.26
2011/0282439	A1	11/2011	Thill et al.	
2011/0319988	A1	12/2011	Schankereli et al.	
2012/0035719	A1	2/2012	Forster et al.	
2012/0046742	A1	2/2012	Tuval et al.	
2012/0078357	A1	3/2012	Conklin	
2012/0083878	A1	4/2012	Sequin	
2012/0179244	A1	7/2012	Schankereli	
2012/0215303	A1	8/2012	Quadri	
2012/0232646	A1	9/2012	Agathos	
2012/0277856	A1	11/2012	Spenser et al.	
2012/0296418	A1	11/2012	Bonyuet	
2012/0316642	A1	12/2012	Yu et al.	
2013/0018458	A1	1/2013	Yohanan et al.	
2013/0023984	A1	1/2013	Conklin	
2013/0150956	A1	6/2013	Yohanan et al.	
2013/0204359	A1	8/2013	Thubrikar et al.	
2013/0211508	A1	8/2013	Lane et al.	
2013/0218267	A1	8/2013	Braido et al.	
2013/0274870	A1	10/2013	Lombardi et al.	
2013/0338765	A1	12/2013	Braido et al.	
2014/0142694	A1	5/2014	Tabor et al.	
2014/0350663	A1	11/2014	Braido et al.	
2014/0350665	A1	11/2014	Braido et al.	
2014/0350667	A1	11/2014	Braido et al.	

FOREIGN PATENT DOCUMENTS

DE	19546692	A1	6/1997
DE	19857887	A1	7/2000
DE	19907646	A1	8/2000
DE	10049812	A1	4/2002
DE	10049813	C1	4/2002
DE	10049814	A1	4/2002
DE	10049815	A1	4/2002
EP	0103546	A1	3/1984
EP	0144167	A2	6/1985
EP	0592410	A1	4/1994
EP	0597967	A1	5/1994
EP	0850607	A1	7/1998
EP	1057460	A1	12/2000
EP	1088529	A2	4/2001
EP	1570809	A1	9/2005
EP	2254513		12/2010
EP	2620125		7/2013
EP	2749254		7/2014
FR	2788217	A1	7/2000
GB	2056023	A	3/1981
JP	2008541865	A	11/2008
JP	2011500241	A	1/2011
JP	2011522634	A	8/2011
JP	2011528256	A	11/2011
JP	2012504031	A	2/2012
SU	158988		11/1963
SU	1271508	A1	11/1986
SU	1371700	A1	2/1988
SU	1457921	A1	2/1989
WO	91/17720	A1	11/1991
WO	92/17118	A1	10/1992
WO	93/01768	A1	2/1993
WO	97/24080	A1	7/1997
WO	98/29057	A1	7/1998
WO	99/33414	A1	7/1999
WO	99/40964	A1	8/1999
WO	99/47075	A1	9/1999
WO	00/18333	A1	4/2000
WO	00/41652	A1	7/2000
WO	00/47139	A1	8/2000
WO	01/35878	A2	5/2001
WO	01/49213	A2	7/2001
WO	01/54624	A1	8/2001
WO	01/54625	A1	8/2001
WO	01/62189	A1	8/2001
WO	01/64137	A1	9/2001
WO	01/76510	A2	10/2001
WO	02/22054	A1	3/2002
WO	02/36048	A1	5/2002
WO	02/41789	A2	5/2002
WO	02/43620	A1	6/2002
WO	02/47575	A2	6/2002
WO	02/49540	A2	6/2002
WO	03/047468	A1	6/2003
WO	2005/087140	A1	9/2005
WO	2006/014233	A2	2/2006
WO	2006/034008	A2	3/2006
WO	2008/005405	A2	1/2008
WO	2008/035337	A2	3/2008
WO	2008/147964	A1	12/2008
WO	2008/150529	A1	12/2008
WO	2009042196	A2	4/2009

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	2009053497	A1	4/2009
WO	WO2009042196	*	4/2009
WO	2009/061389	A2	5/2009
WO	2009149462	A2	12/2009
WO	2010008548	A2	1/2010
WO	2010037141	A1	4/2010
WO	WO2010/141847		12/2010
WO	2012032187	A1	3/2012
WO	WO 2012/032187		3/2012
WO	WO 2012/161786		11/2012

OTHER PUBLICATIONS

Andersen, et al., "Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs." European Heart Journal (1992), 13, 704-708.

Andersen, Henning Rud, "History of Percutaneous Aortic Valve Prosthesis," Herz 34 2009 Nr. 5, Urban & Vogel, pp. 343-346, Skejby University Hospital Department of Cardiology, Aarhus, Denmark.

Almagor, M.D., Yaron, et al., "Balloon Expandable Stent Implantation in Stenotic Right Heart Valved Conduits," Journal of the American College of Cardiology, vol. 16, No. 6, pp. 1310-1314, Nov. 1, 1990; ISSN 0735-1097.

Sabbah, Ph.D., Hani N., et al., "Mechanical Factors in the Degeneration of Porcine Bioprosthetic Valves: An Overview," Journal of Cardiac Surgery, vol. 4, No. 4, pp. 302-309, Dec. 1989; ISSN 0886-0440.

Serruys, P.W., et al., "Stenting of Coronary Arteries. Are we the Sorcerer's Apprentice?," European Heart Journal (1989) 10, 774-782, pp. 37-45, Jun. 13, 1989.

Kolata, Gina, "Device That Opens Clogged Arteries Gets a Failing Grade in a New Study," nytimes.com, http://www.nytimes.com/1991/01/03/health/device-that-opens-clogged-arteries-gets-a-faili . . . , Jul. 29, 2009, 2 pages.

Urban, M.D., Philip, "Coronary Artery Stenting," Editions Médecine et Hygiène, Genève, 1991, pp. 5-47.

Al-Khaja, N., et al., "Eleven Years' Experience with Carpentier-Edwards Biological Valves in Relation to Survival and Complications," European Journal of Cardiothoracic Surgery 3:305-311, Jun. 30, 2009.

Wheatley, M.D., David J., "Valve Prostheses," Rob & Smith's Operative Surgery, Fourth Edition, pp. 415-424, Butterworths 1986.

Benchimol, Alberto, et al., "Simultaneous Left Ventricular Echocardiography and Aortic Blood Velocity During Rapid Right Ventricular Pacing in Man," The American Journal of the Medical Sciences, Jan.-Feb. 1977 vol. 273, No. 1, pp. 55-62.

Watt, A.H., et al. "Intravenous Adenosine in the Treatment of Supraventricular Tachycardia; a Dose-Ranging Study and Interaction with Dipyridamole," British Journal of Clinical Pharmacology (1986), 21, 227-230.

Uchida, Barry T., et al., "Modifications of Gianturco Expandable Wire Stents," AJR:150, May 1988, Dec. 3, 1987, pp. 1185-1187.

Selby, M.D., J. Bayne, "Experience with New Retrieval Forceps for Foreign Body Removal in the Vascular, Urinary, and Biliary Systems," Radiology 1990; 176:535-538.

Inoune, M.D., Kanji, et al., "Clinical Application of Transvenous Mitral Commissurotomy by a New Balloon Catheter," The Journal of Thoracic and Cardiovascular Surgery 87:394-402, 1984.

Al Zaibag, Muayed, et al., "Percutaneous Balloon Valvotomy in Tricuspid Stenosis," British Heart Journal, Jan. 1987, vol. 57, No. 1, pp. 51-53.

Lawrence, Jr., M.D., David D., "Percutaneous Endovascular Graft: Experimental Evaluation," Radiology 1897; 163: 357-360.

Dotter, M.D., Charles T., "Transluminal Treatment of Arteriosclerotic Obstruction," University of Oregon's Minthorn Memorial Laboratory for Cardiovascular Research through Radiology, Circulation, vol. XXX, Nov. 1964, pp. 654-670.

Sigwart, Ulrich, "An Overview of Intravascular Stents: Old and New," Chapter 48, Textbook of Interventional Cardiology, 2nd Edition, W.B. Saunders Company, Philadelphia, PA, © 1994, 1990, pp. 803-815.

Rashkind, M.D., William J., "Historical Aspects of Interventional Cardiology: Past, Present, Future," Texas Heart Institute Journal, Interventional Cardiology, pp. 363-367.

Rösch, M.D., Josef, "The Birth, Early Years and Future of Interventional Radiology," J Vasc Interv Radiol 2003; 14:841-853.

Pavcnik, M.D., Ph.D., Dusan, et al. "Development and Initial Experimental Evaluation of a Prosthetic Aortic Valve for Transcatheter Placement," Cardiovascular Radiology 1992; 183:151-154.

Ross, F.R.C.S., D.N., "Aortic Valve Surgery," Guy's Hospital, London, pp. 192-197, approximately 1968.

Rashkind, M.D., William J., "Creationof an Atrial Septal Defect Withoput Thoracotomy," the Journal of the American Medical Association, vol. 196, No. 11, Jun. 13, 1966, pp. 173-174.

Porstmann, W., et al., "Der Verschluß des Ductus Arteriosus Persistens ohne Thorakotomie," Thoraxchirurgie Vaskuläre Chirurgie, Band 15, Heft 2, Stuttgart, im Apr. 1967, pp. 199-203.

Curriculum Vitae of Robert A. Ersek, M.D., FACS, Jul. 10, 2009, http://www.ersek.com/rae-cv.htm.

* cited by examiner

FIG. 1

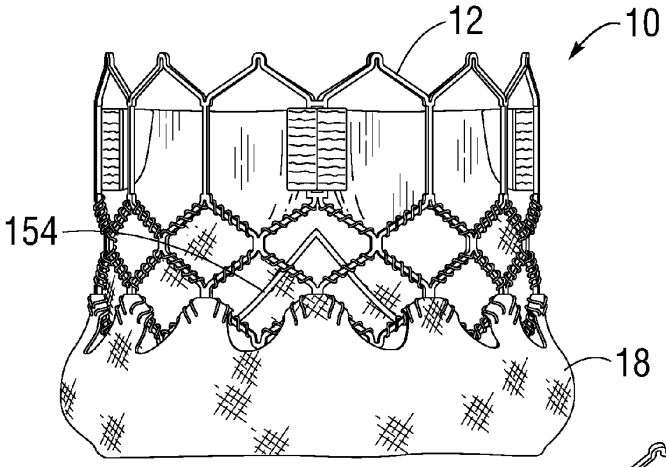


FIG. 2

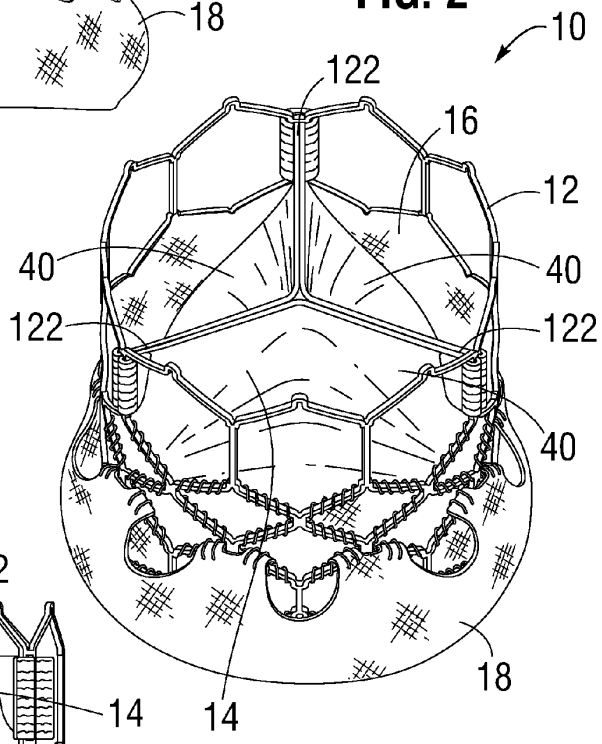
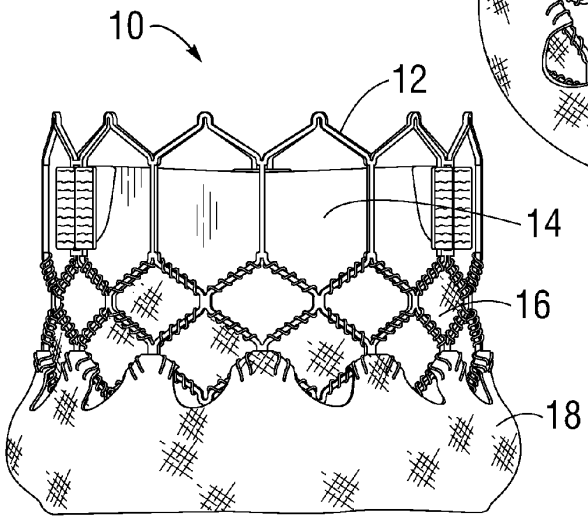


FIG. 3



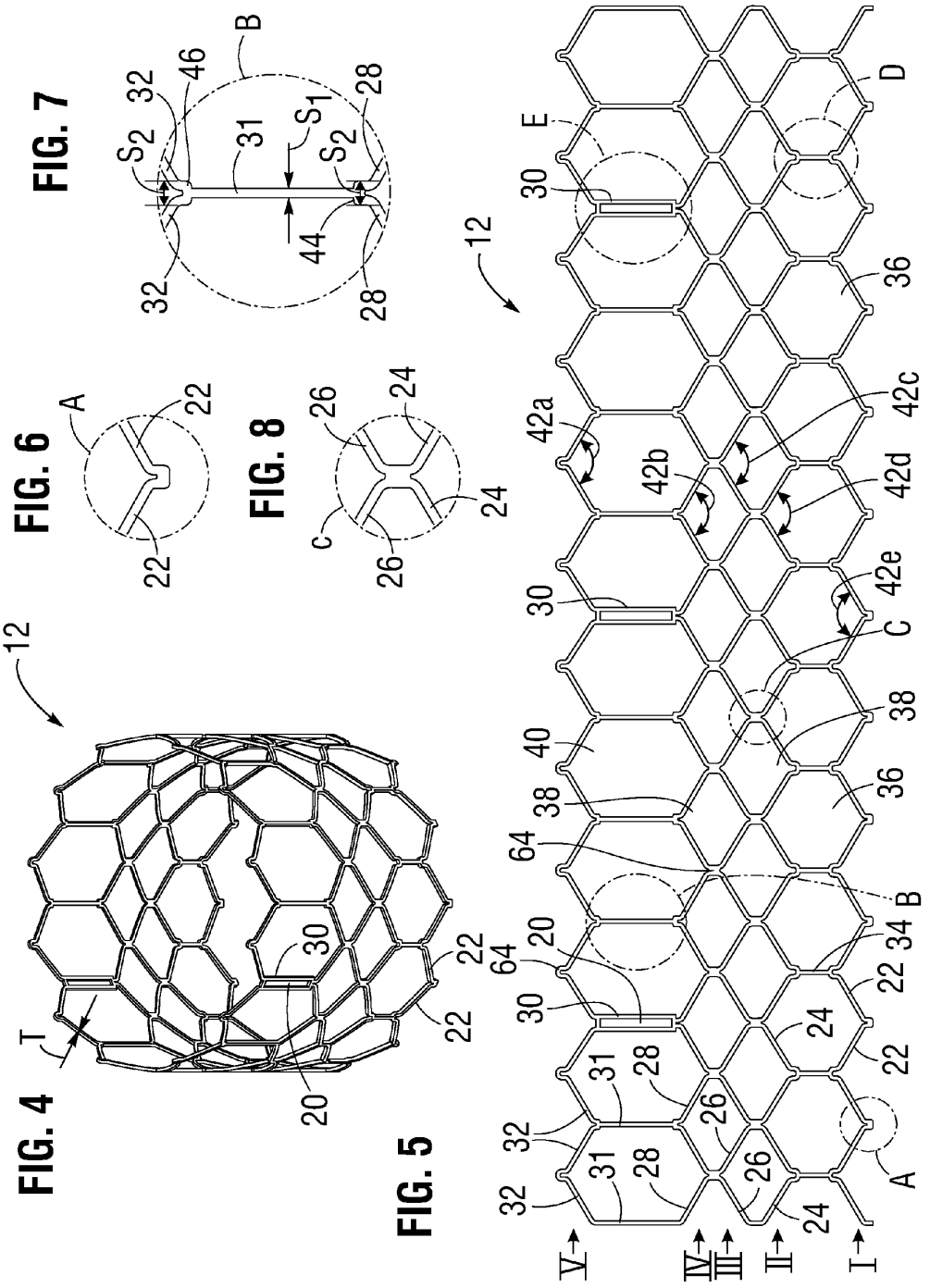


FIG. 7
FIG. 6
FIG. 8
FIG. 4
FIG. 5
12
A
B
C
D
E
20
22
24
26
28
30
31
32
36
38
40
42a
42b
42c
42d
42e
44
46
64
S1
S2
T
I
II
III
IV
V

FIG. 9

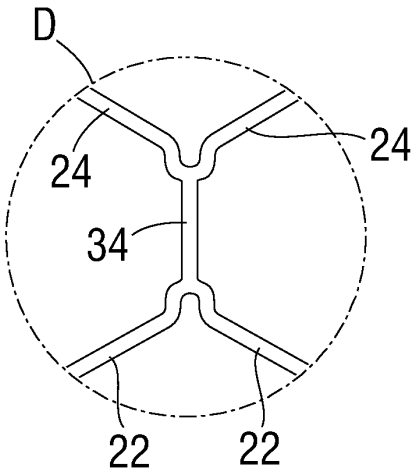


FIG. 10

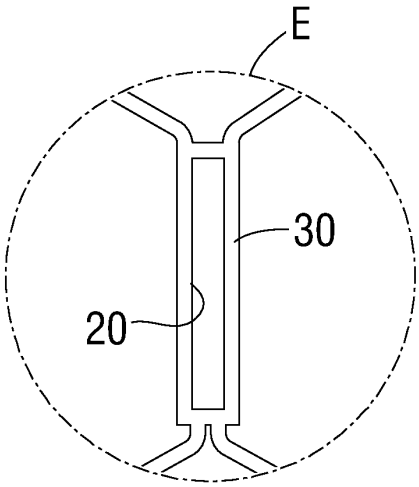


FIG. 11

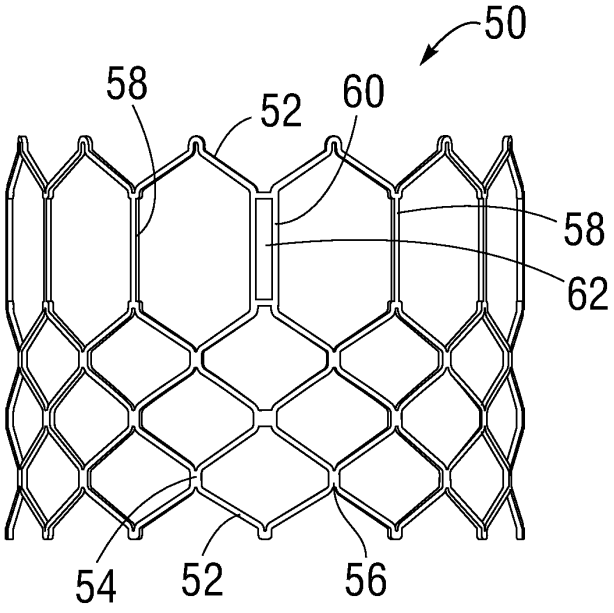


FIG. 12

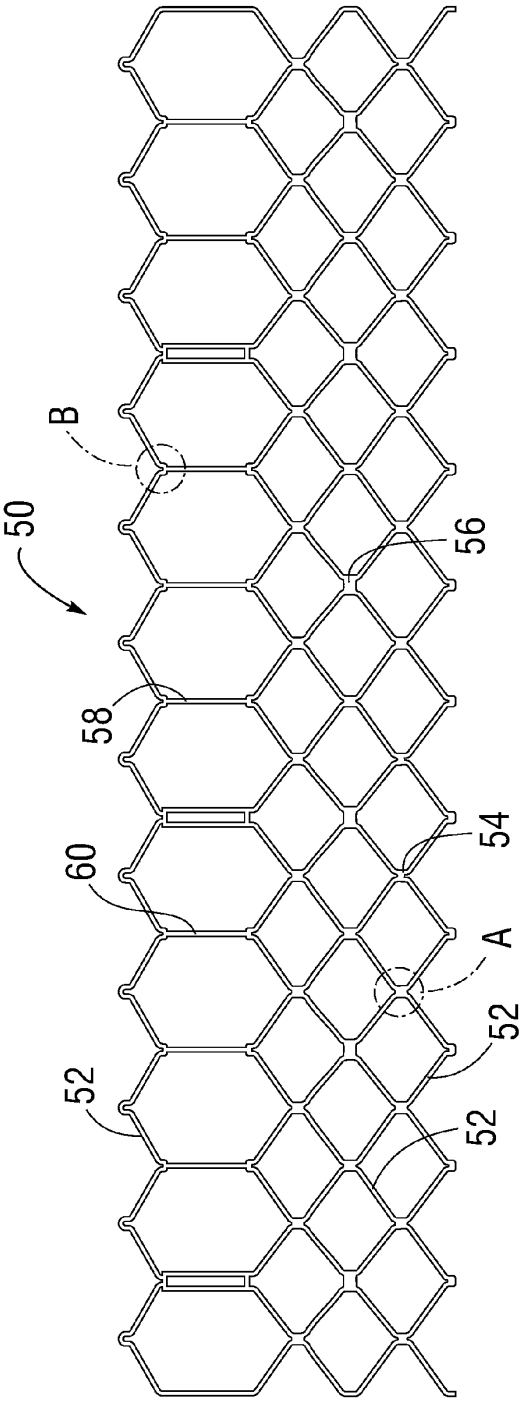


FIG. 15B

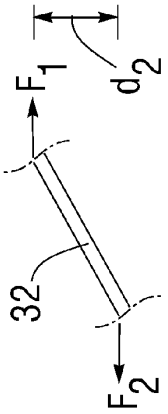


FIG. 15A

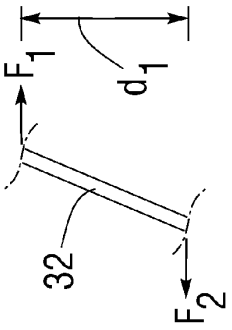


FIG. 14

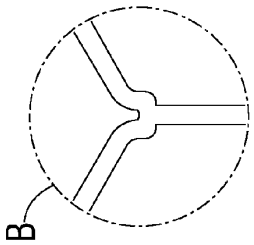


FIG. 13

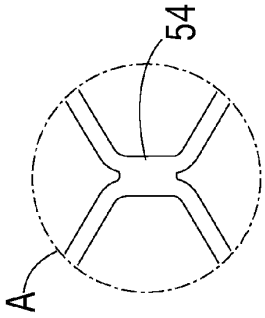


FIG. 16A

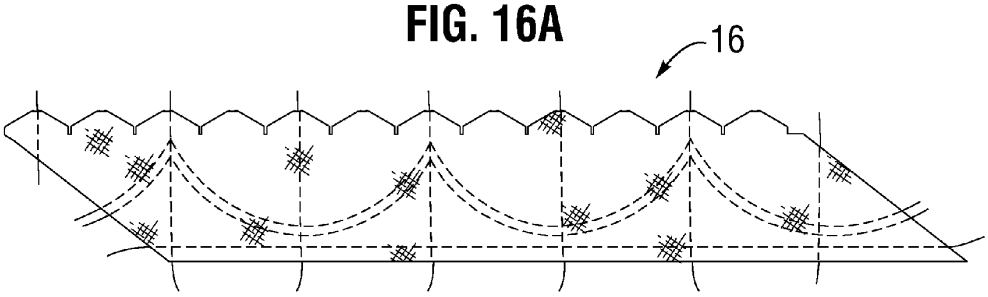


FIG. 16B

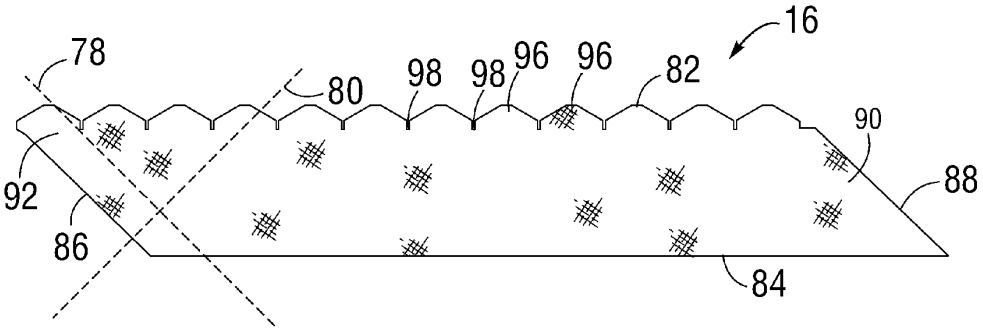


FIG. 17

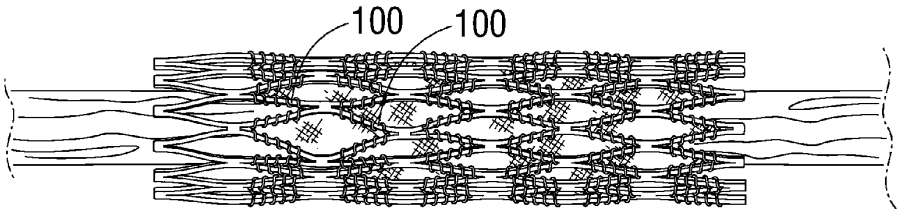


FIG. 18

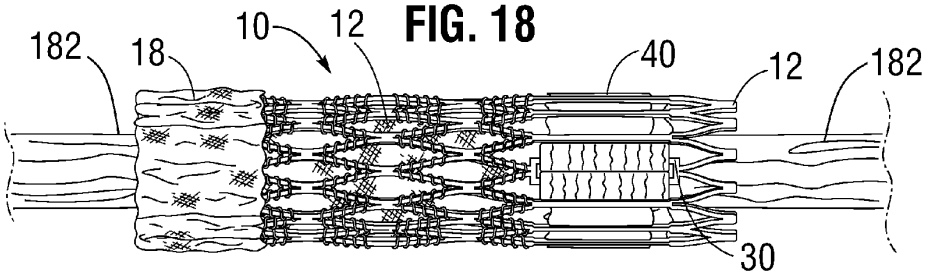


FIG. 19A

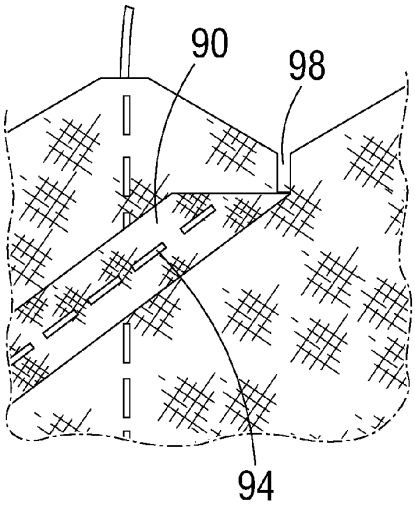


FIG. 19B

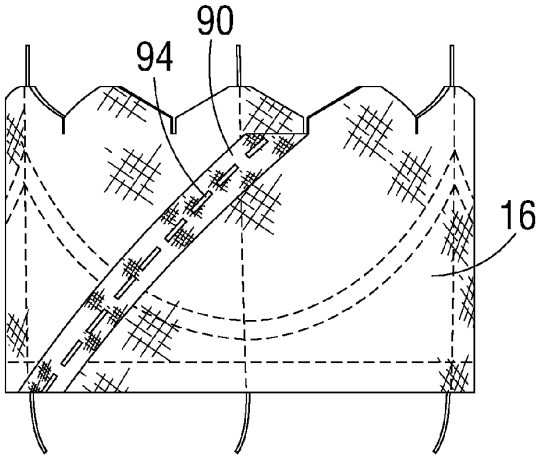


FIG. 20

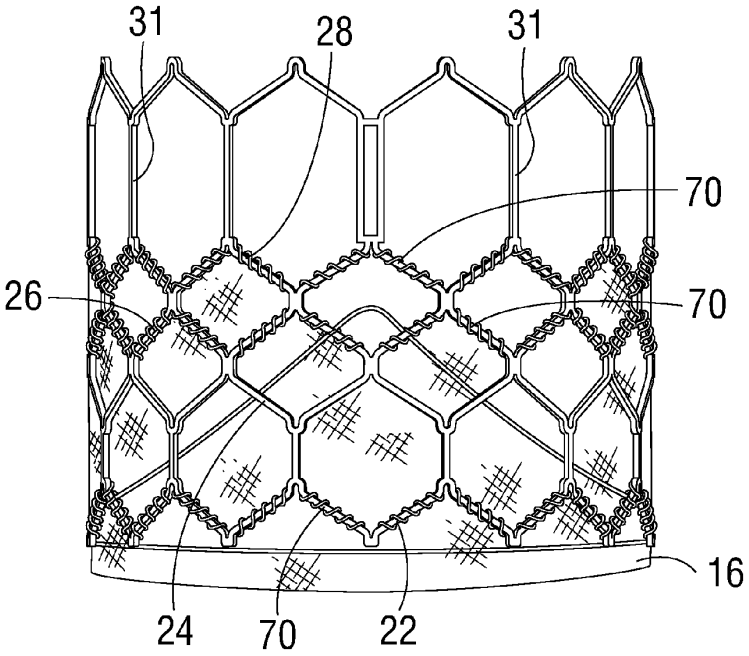


FIG. 21

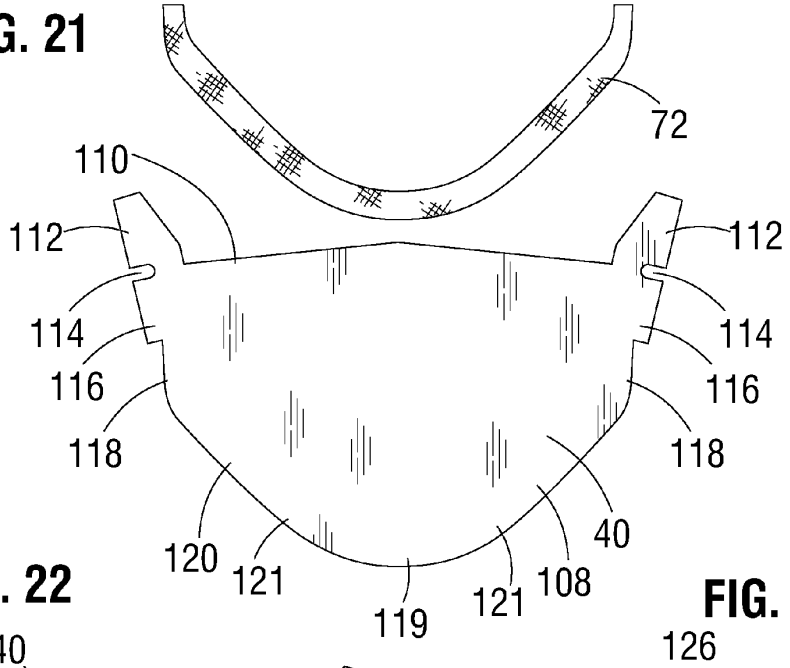


FIG. 22

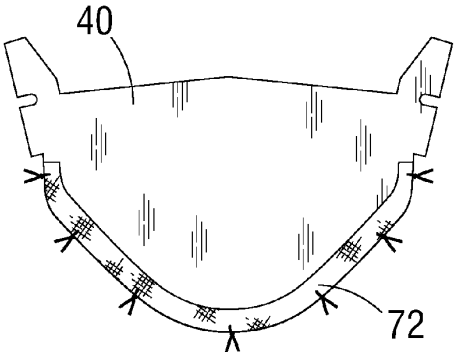


FIG. 23

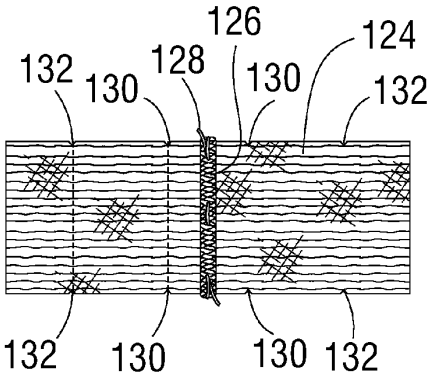


FIG. 24

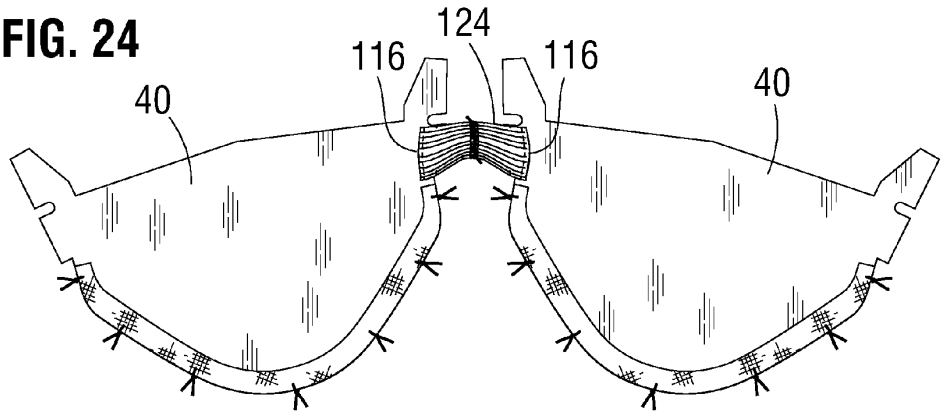


FIG. 25

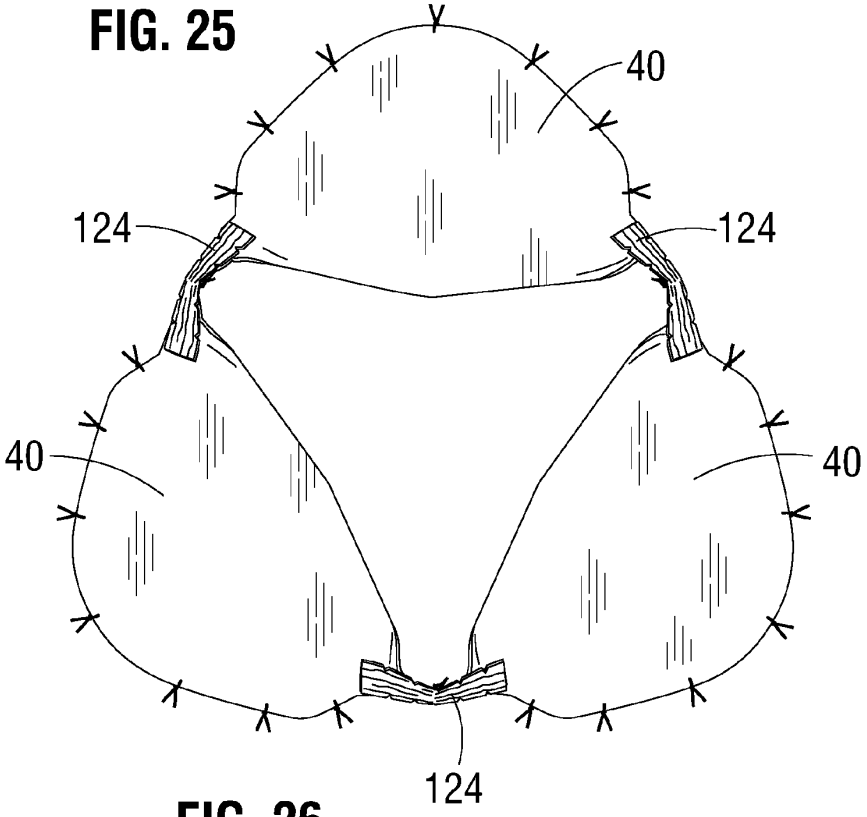


FIG. 26

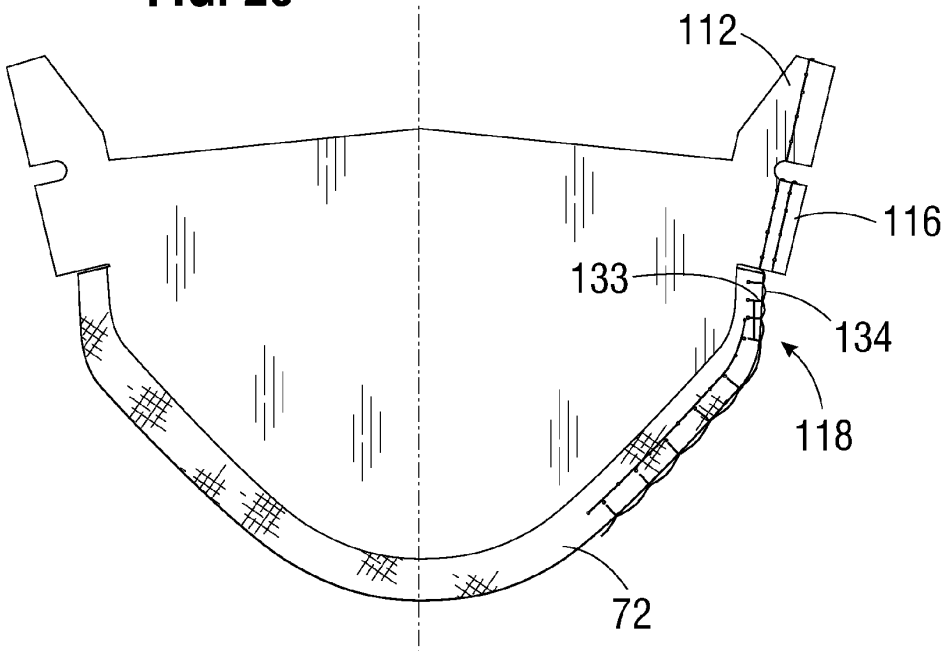


FIG. 27

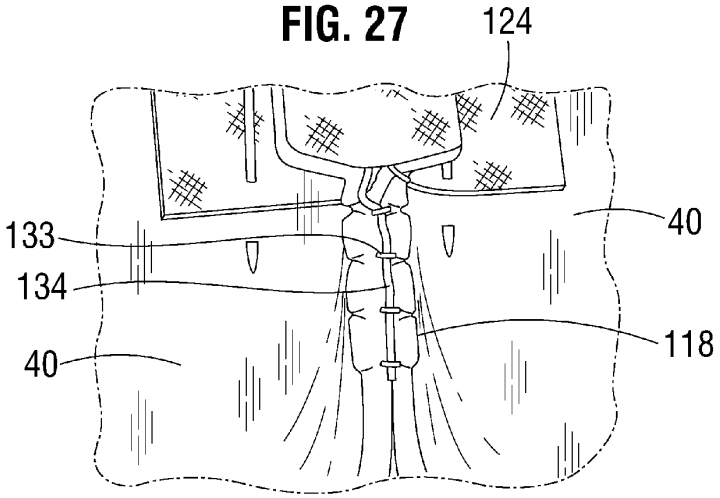


FIG. 28

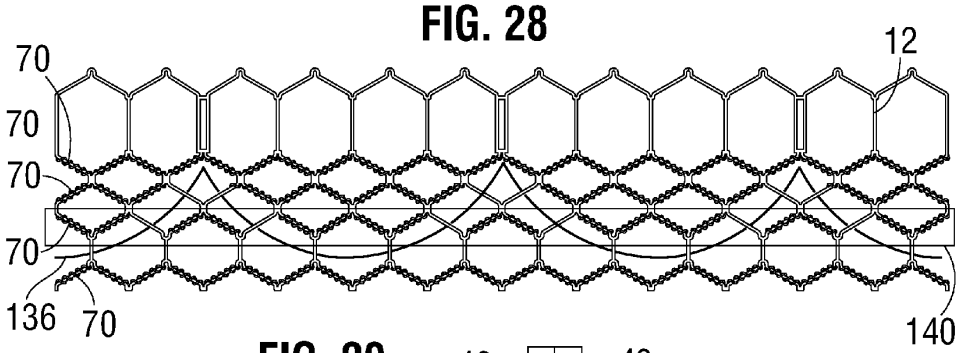


FIG. 29

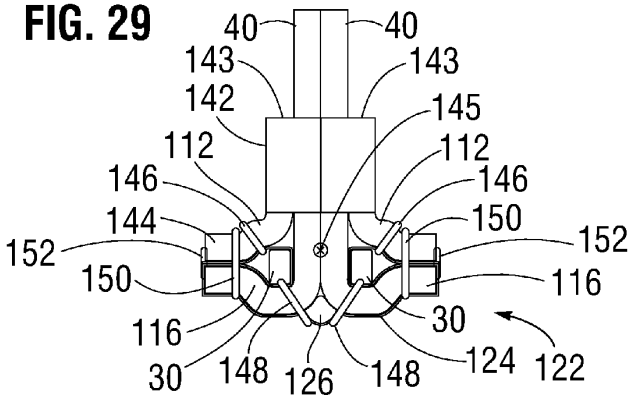


FIG. 30

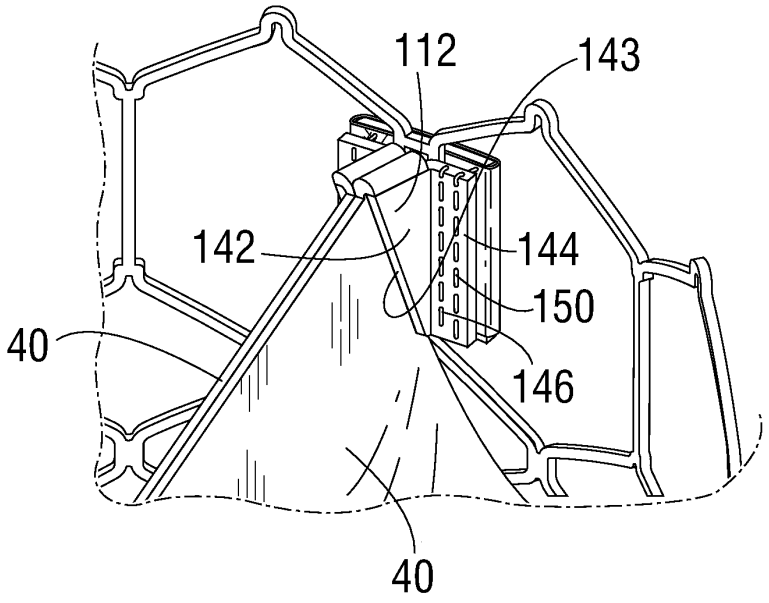


FIG. 31

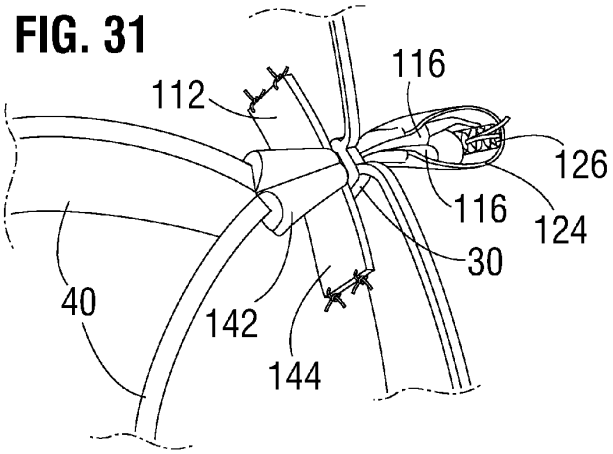


FIG. 32

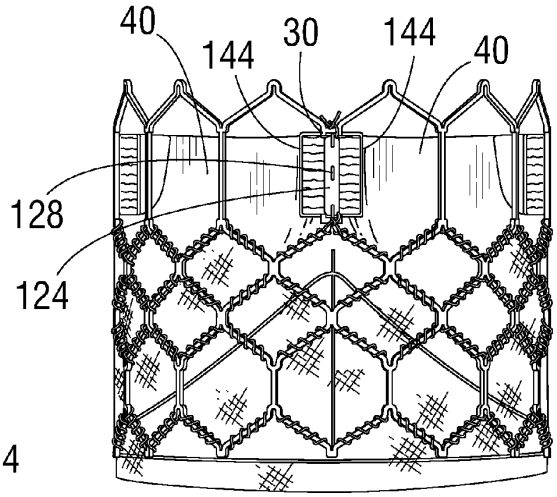


FIG. 33

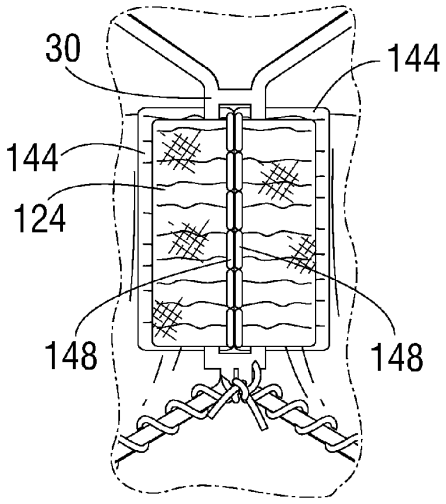


FIG. 34

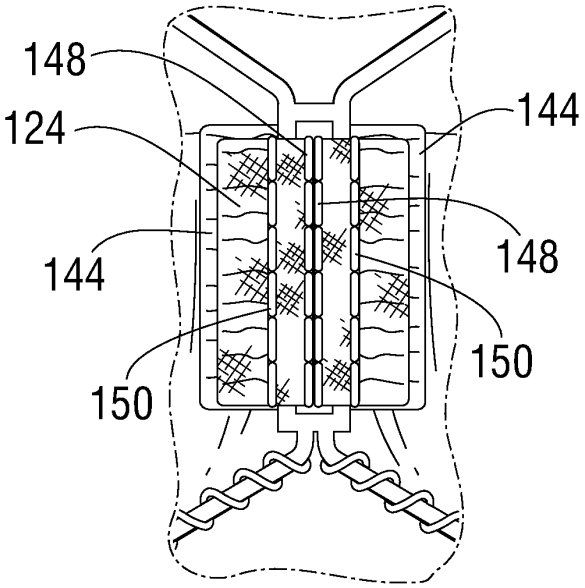


FIG. 35

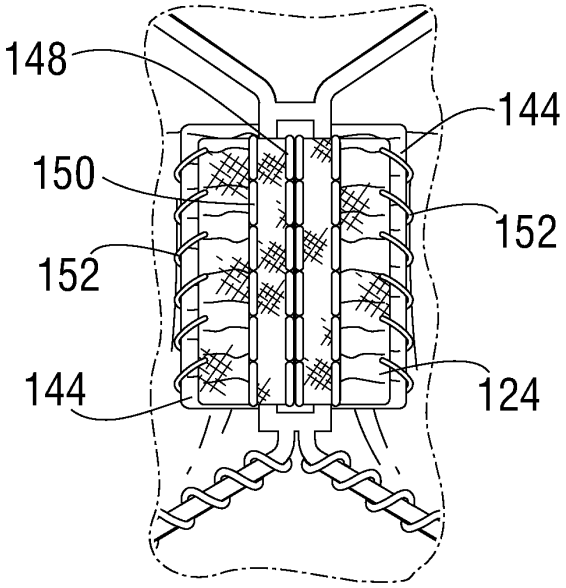


FIG. 36

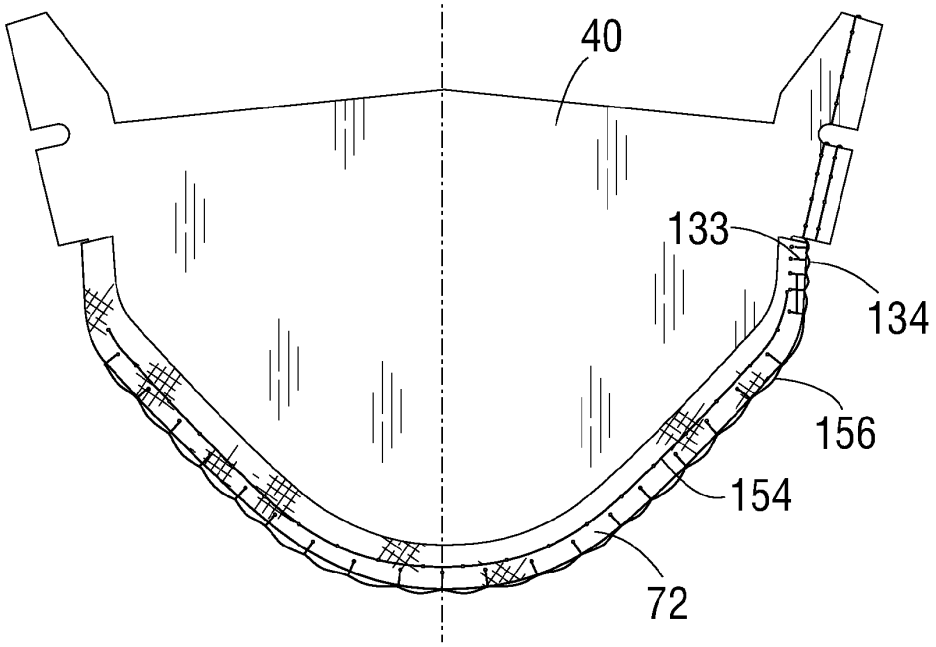


FIG. 37

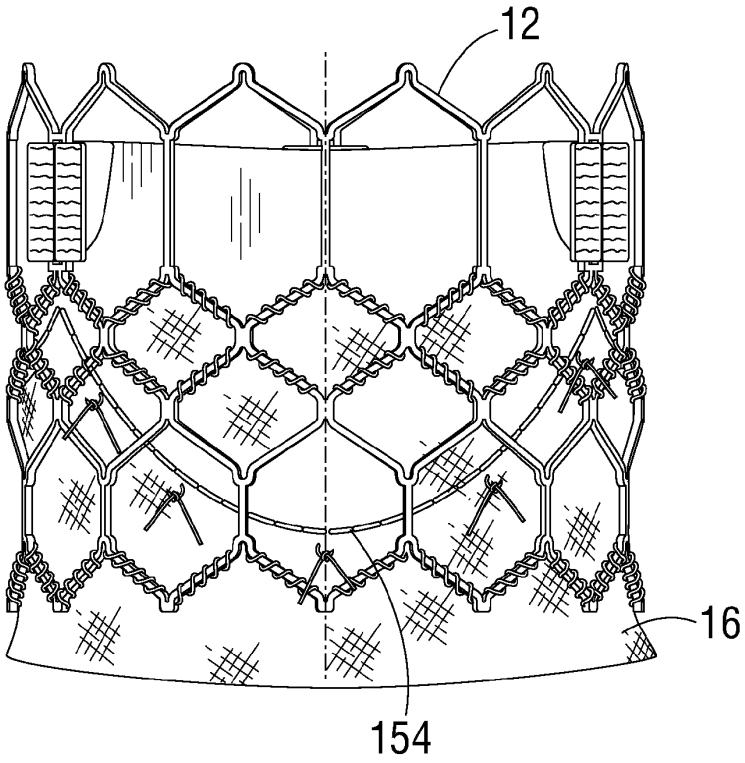


FIG. 38

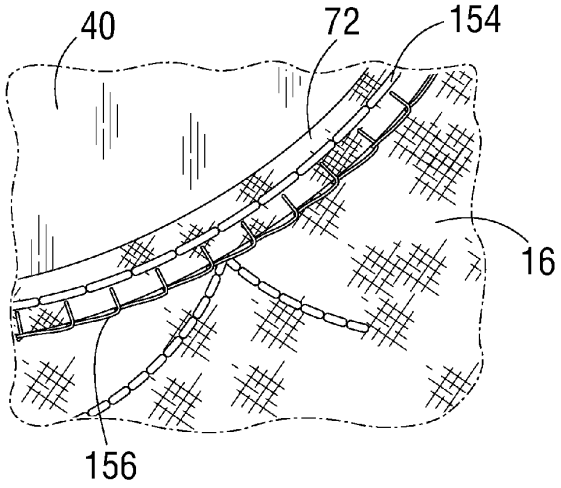


FIG. 39

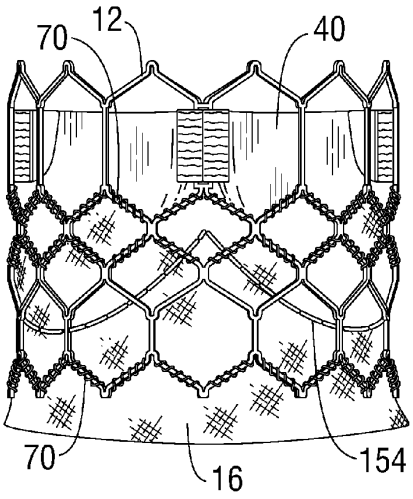


FIG. 40

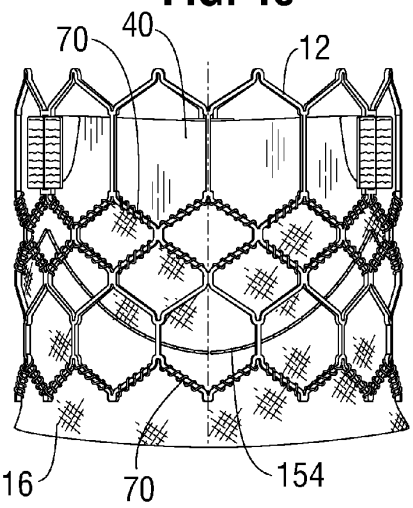


FIG. 41

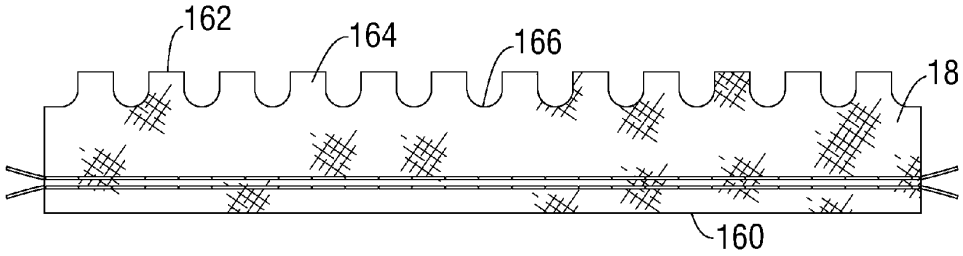


FIG. 43

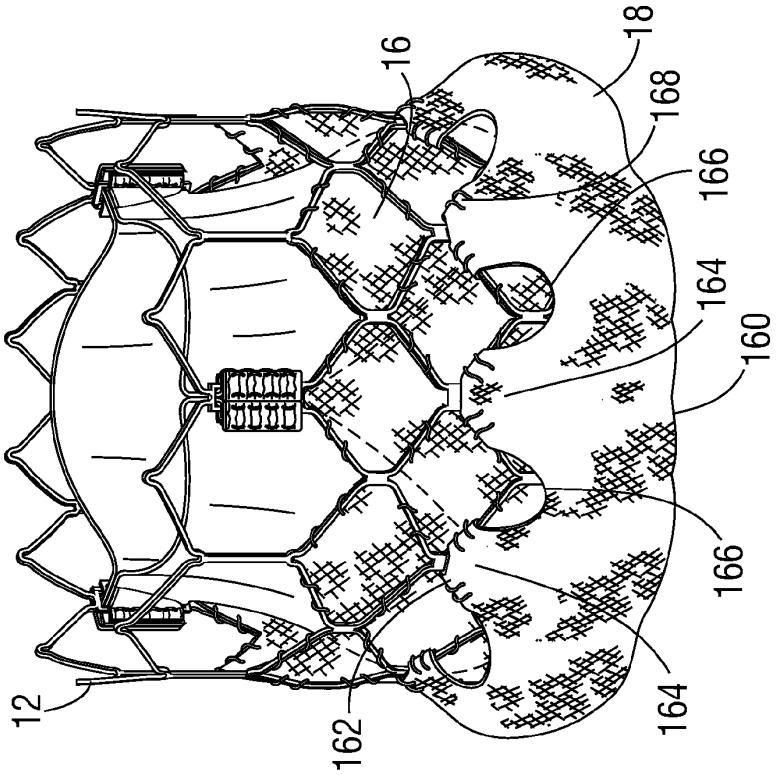


FIG. 42

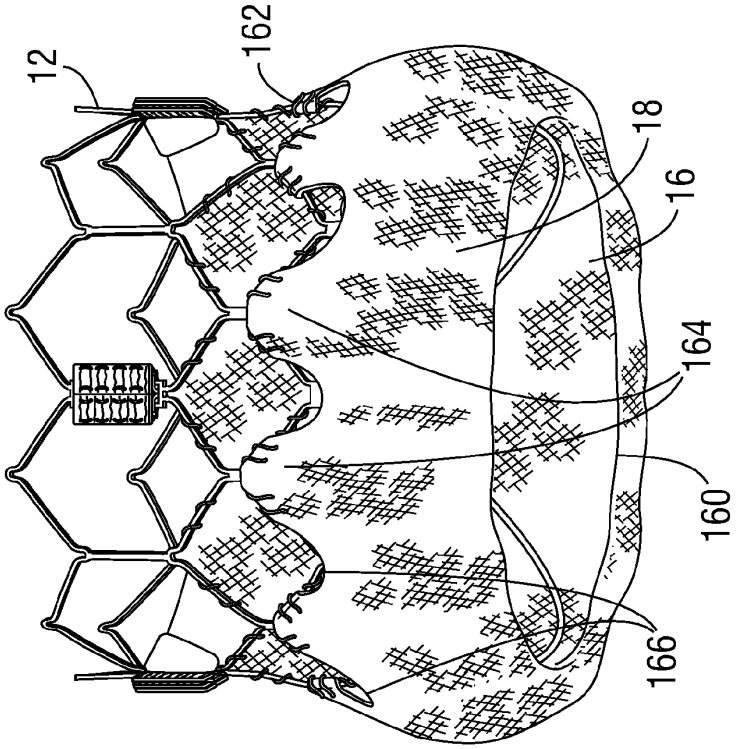


FIG. 44

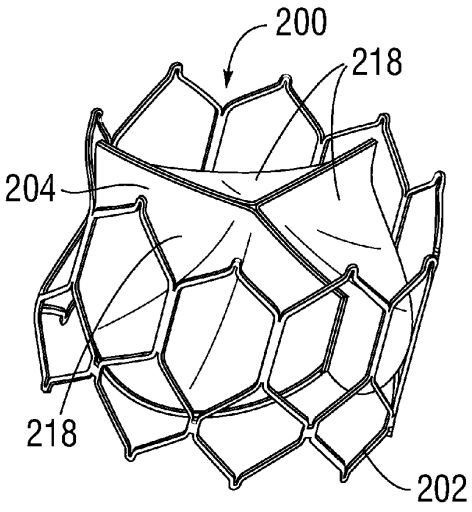


FIG. 45

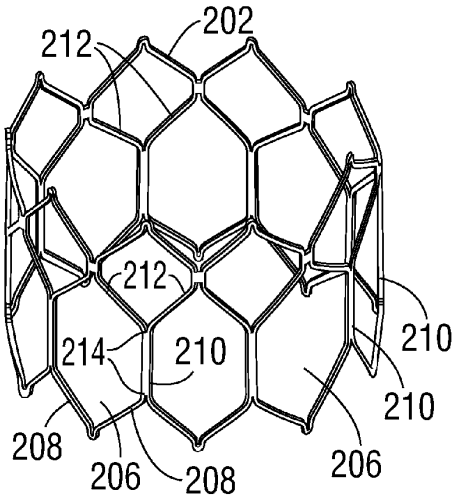


FIG. 46

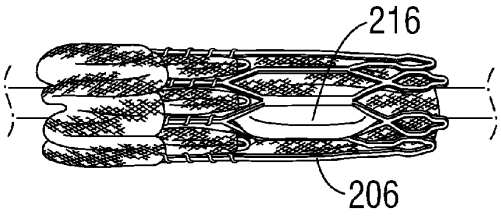


FIG. 47

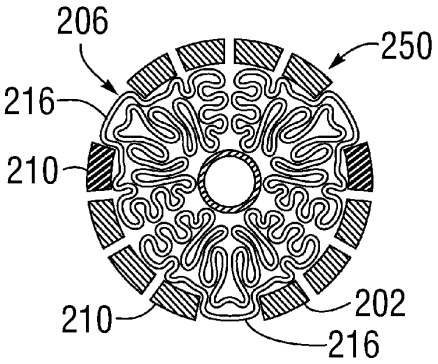


FIG. 48

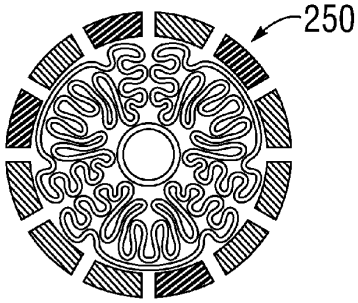


FIG. 49

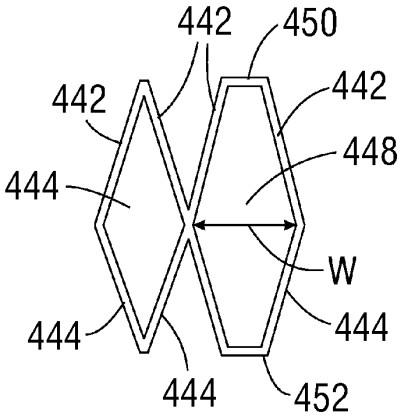


FIG. 50

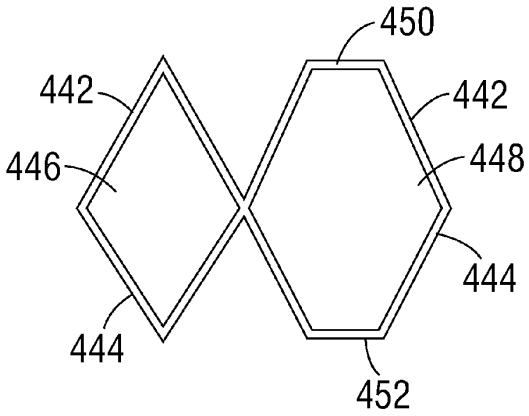


FIG. 51

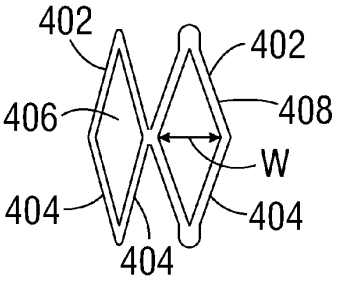


FIG. 52

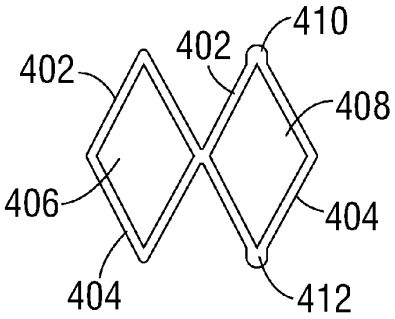


FIG. 53

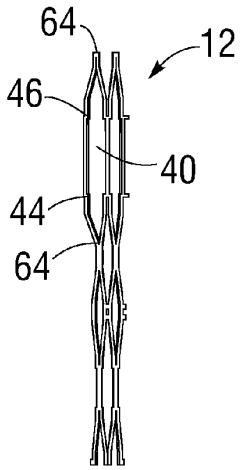


FIG. 54

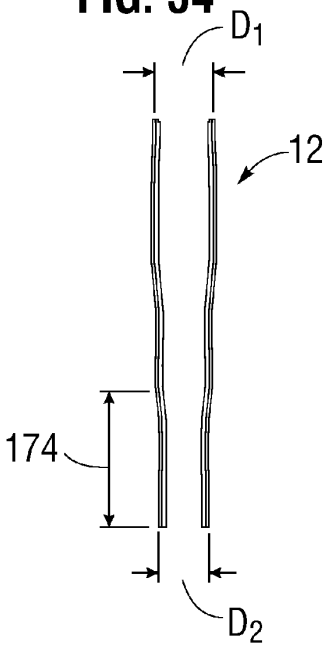


FIG. 55

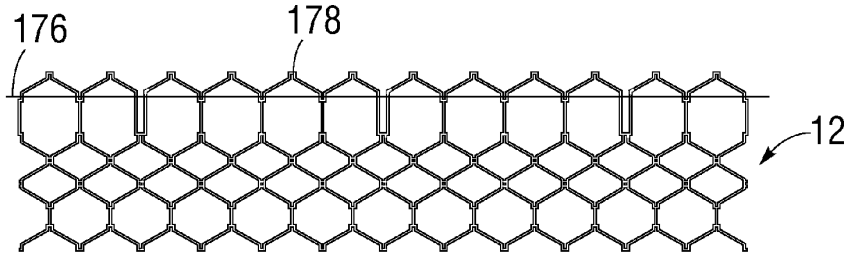


FIG. 56

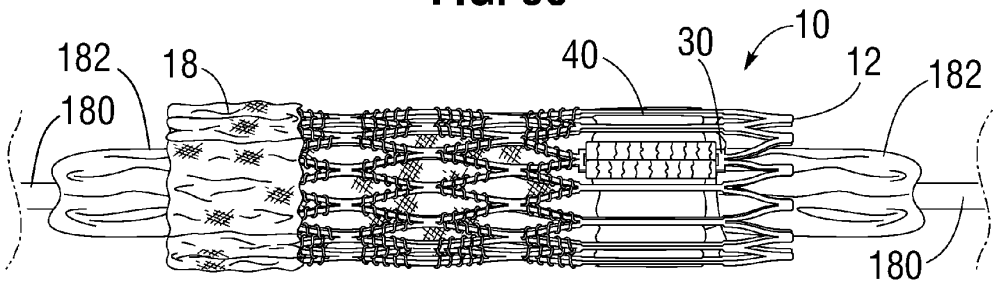


FIG. 57

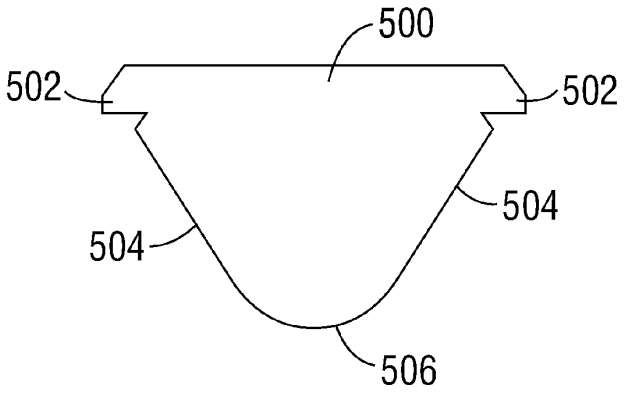


FIG. 58

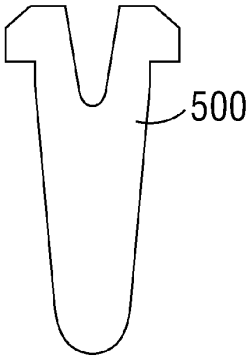
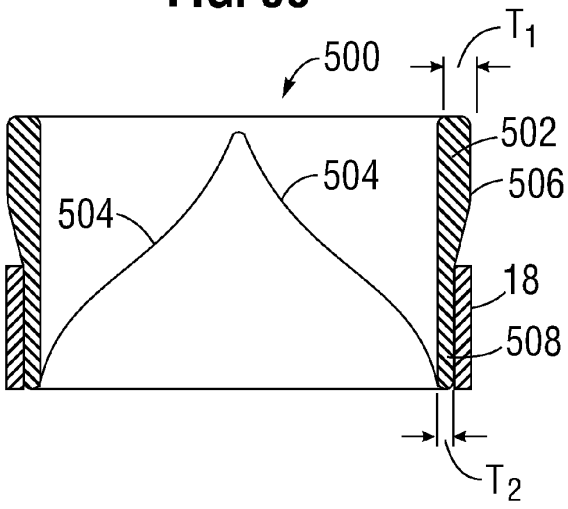


FIG. 59



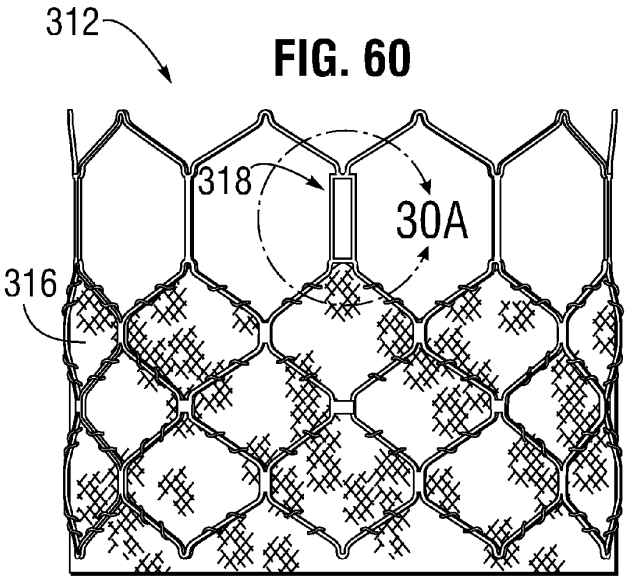


FIG. 60

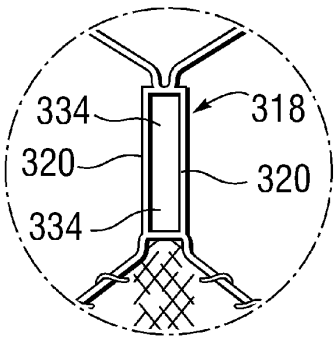


FIG. 60A

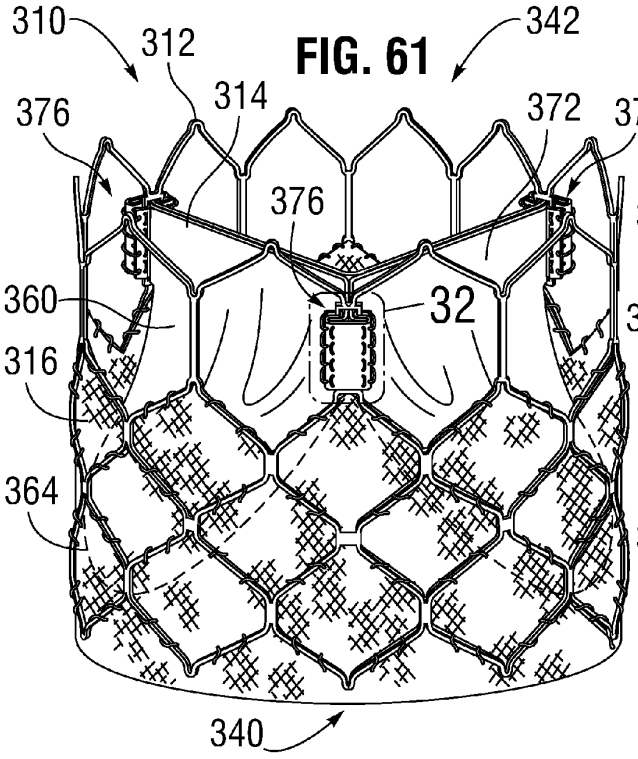


FIG. 61

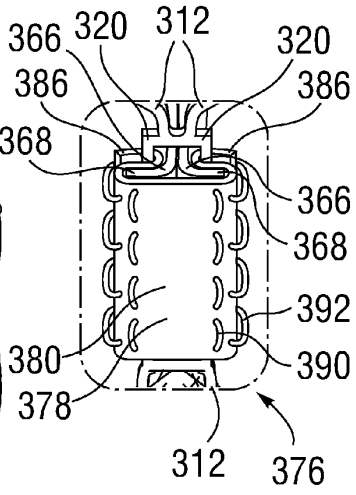


FIG. 62

FIG. 63

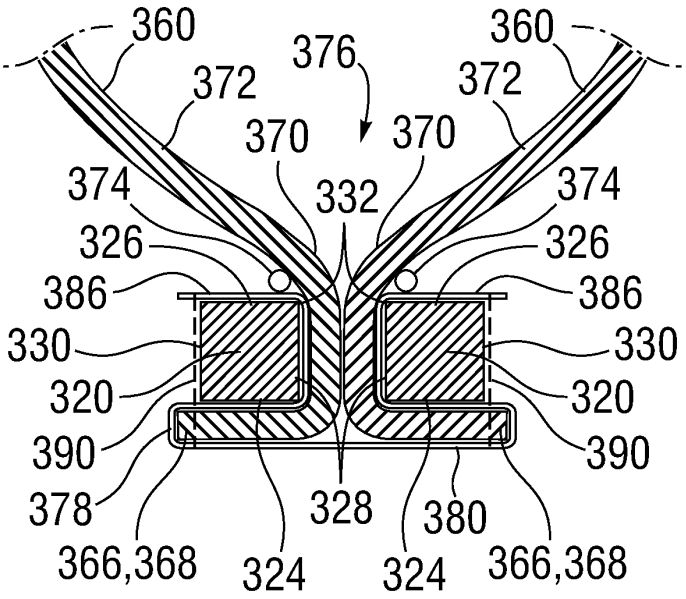

360
376
360
372
372
370
370
374
332
374
326
326
386
386
330
330
320
320
390
390
378
328
380
366,368
324
324
366,368

FIG. 64

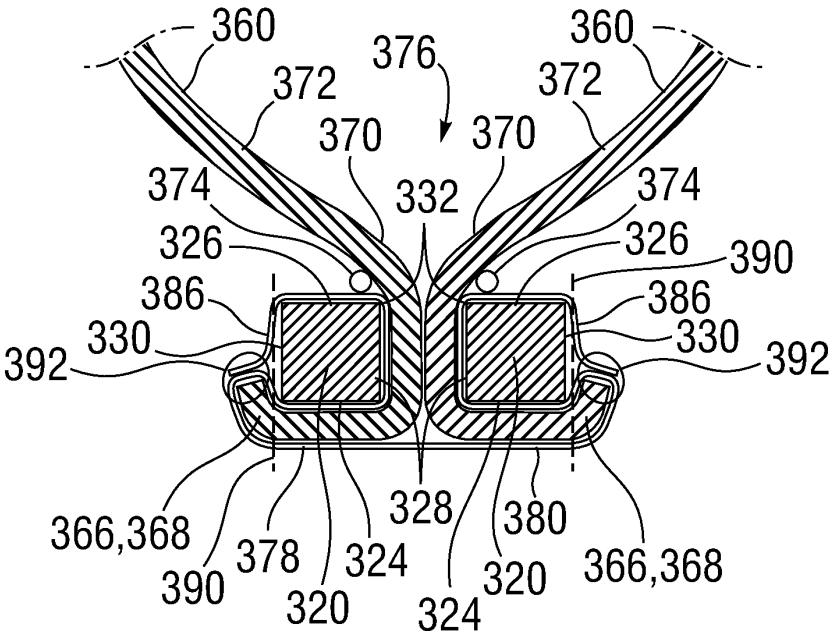

360
376
360
372
372
370
370
374
332
374
326
326
390
386
386
330
330
392
392
366,368
328
380
390
378
324
320
320
366,368
324

FIG. 65

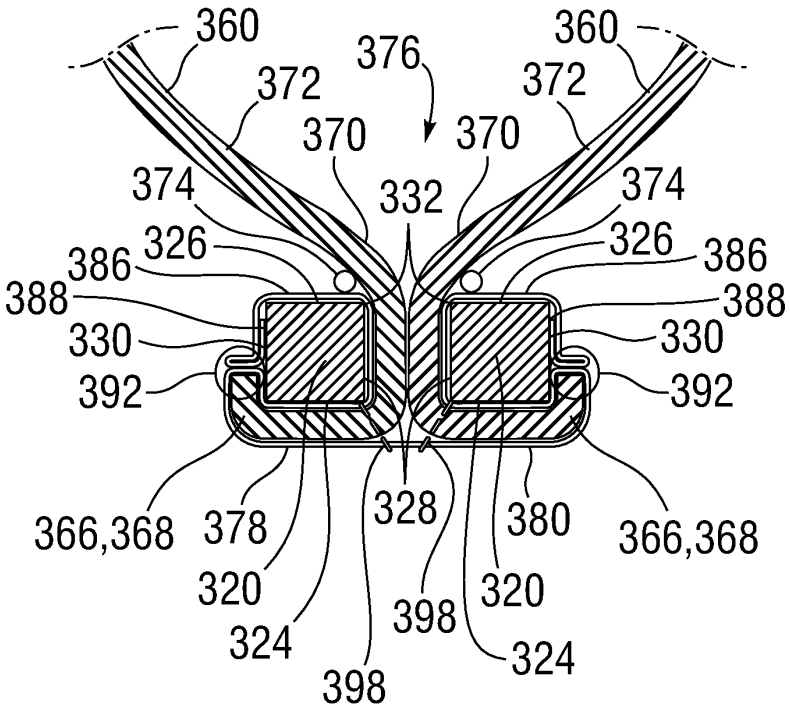

360
376
360
372
372
370
370
374
332
374
326
326
386
386
388
388
330
330
392
392
366,368
378
328
380
366,368
320
320
398
324
324
398

FIG. 66

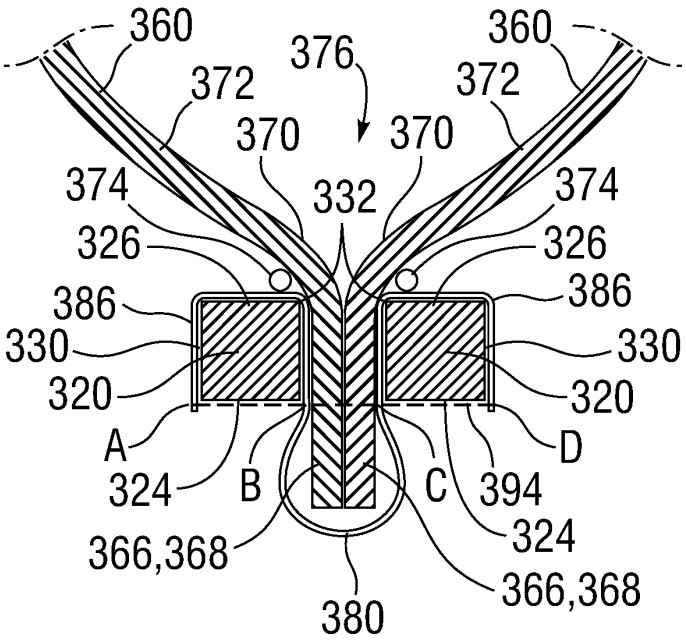

360
376
360
372
372
370
370
374
332
374
326
326
386
386
330
330
320
320
A
D
324
B
C
394
324
366,368
366,368
380

FIG. 67

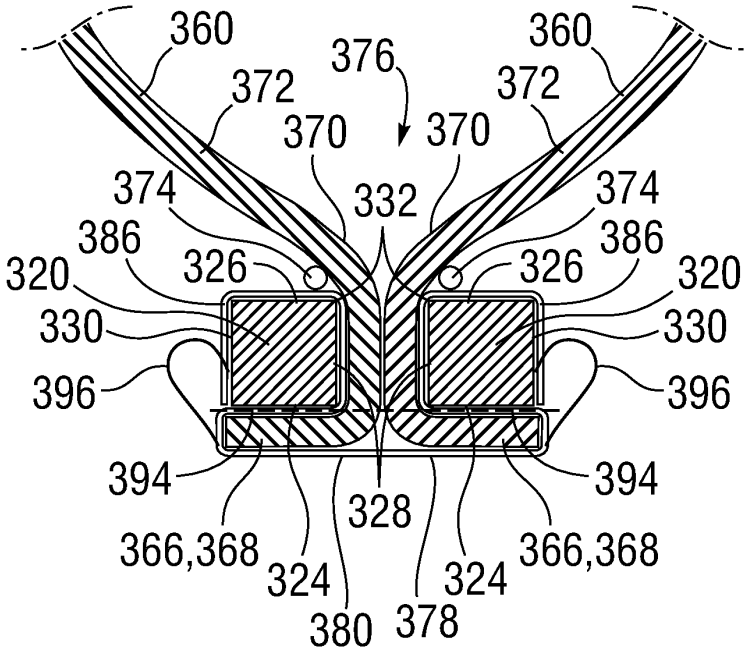

360
376
360
372
372
370
370
374
332
374
386
386
320
326
326
320
330
330
396
396
394
394
328
366,368
366,368
324
324
380
378

FIG. 68

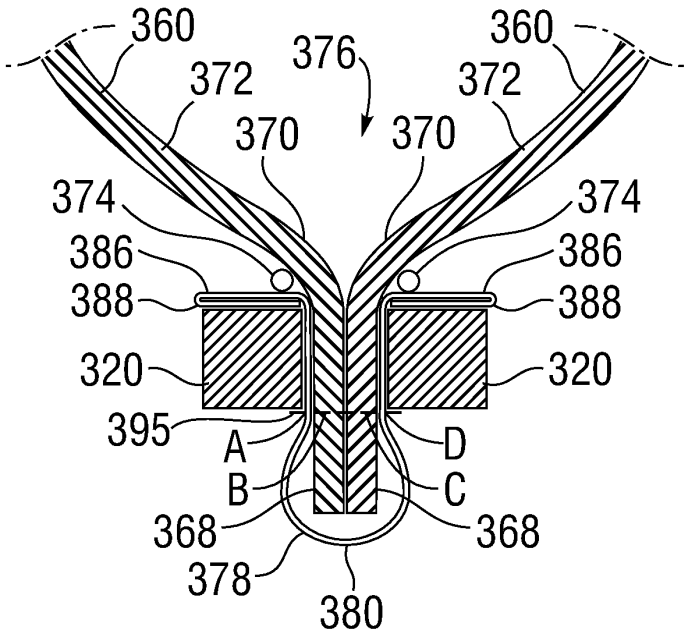

360
372
376
360
372
370
370
374
374
386
386
388
388
320
320
395
A
D
B
C
368
368
378
380

FIG. 69

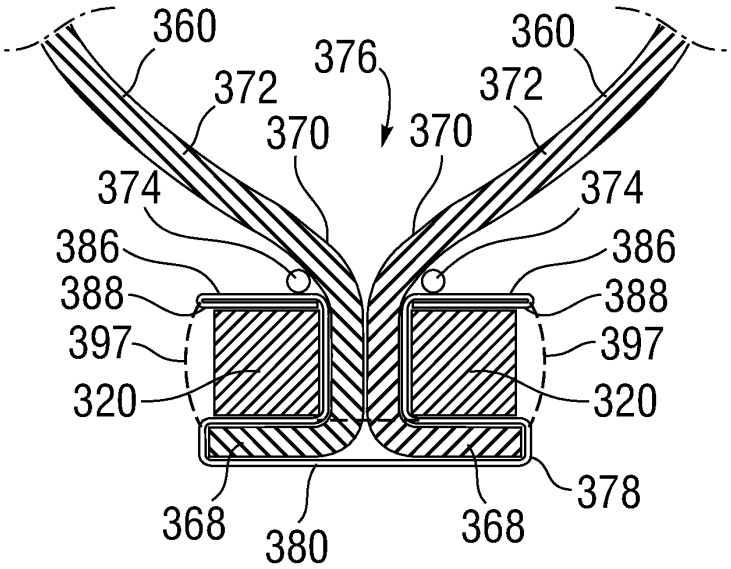

360
372
376
360
372
370
370
374
374
386
386
388
388
397
397
320
320
378
368
380
368

FIG. 70

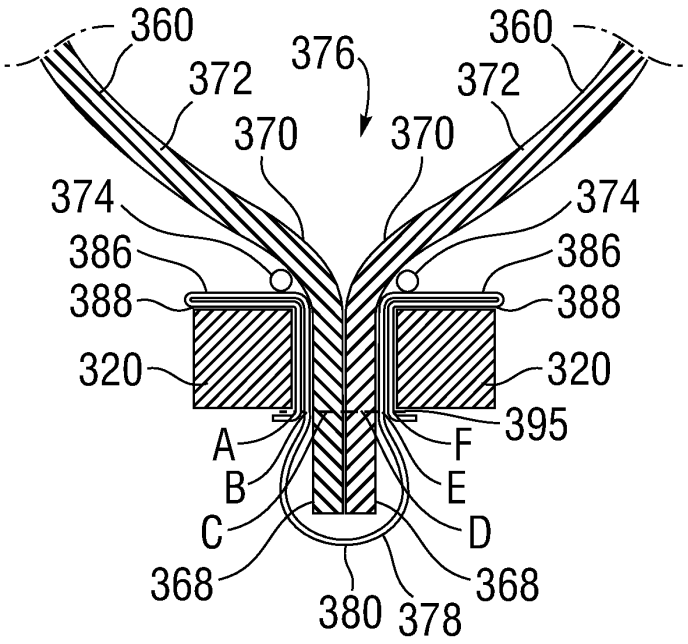
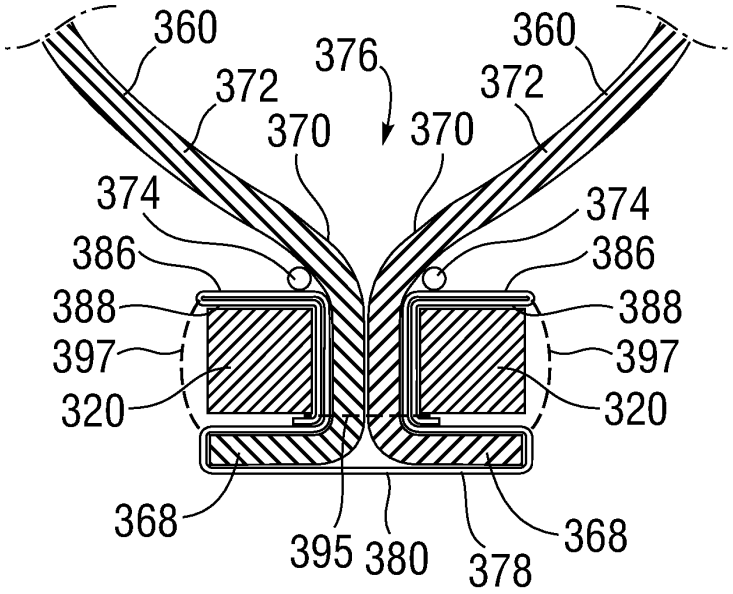

360
372
376
360
372
370
370
374
374
386
386
388
388
320
320
395
A
F
B
E
C
D
368
368
380
378

FIG. 71


360
372
376
360
372
370
370
374
374
386
386
388
388
397
397
320
320
368
368
395
380
378

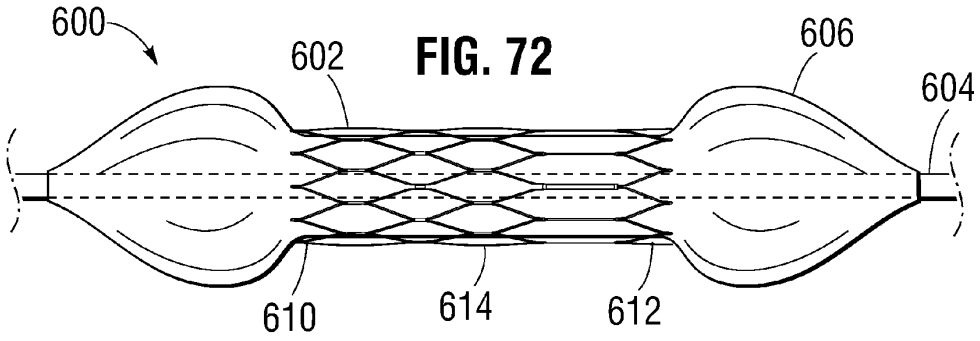


FIG. 72

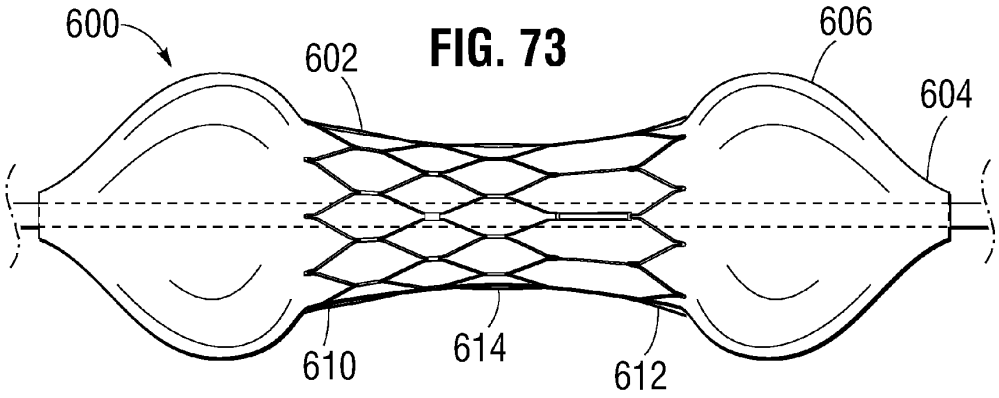


FIG. 73

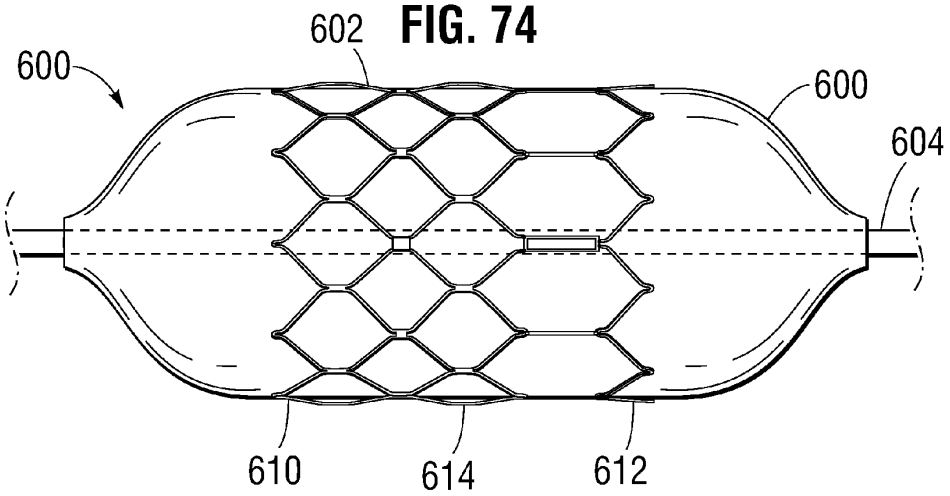


FIG. 74

PROSTHETIC HEART VALVE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/390,107, entitled "COMMISSURE ATTACHMENT FOR PROSTHETIC VALVE," filed Oct. 5, 2010, and U.S. Provisional Application No. 61/508,513, entitled "PROSTHETIC HEART VALVE," filed Jul. 15, 2011, both of which applications are herein incorporated by reference.

FIELD

The present disclosure concerns embodiments of a prosthetic heart valve, and delivery systems for implanting heart valves.

BACKGROUND

The human heart can suffer from various valvular diseases. These valvular diseases can result in significant malfunctioning of the heart and ultimately require replacement of the native valve with an artificial valve. There are a number of known artificial valves and a number of known methods of implanting these artificial valves in humans.

Various surgical techniques may be used to replace or repair a diseased or damaged valve. Due to stenosis and other heart valve diseases, thousands of patients undergo surgery each year wherein the defective native heart valve is replaced by a prosthetic valve. Another less drastic method for treating defective valves is through repair or reconstruction, which is typically used on minimally calcified valves. The problem with surgical therapy is the significant risk it imposes on these chronically ill patients with high morbidity and mortality rates associated with surgical repair.

When the native valve is replaced, surgical implantation of the prosthetic valve typically requires an open-chest surgery during which the heart is stopped and patient placed on cardiopulmonary bypass (a so-called "heart-lung machine"). In one common surgical procedure, the diseased native valve leaflets are excised and a prosthetic valve is sutured to the surrounding tissue at the valve annulus. Because of the trauma associated with the procedure and the attendant duration of extracorporeal blood circulation, some patients do not survive the surgical procedure or die shortly thereafter. It is well known that the risk to the patient increases with the amount of time required on extracorporeal circulation. Due to these risks, a substantial number of patients with defective native valves are deemed inoperable because their condition is too frail to withstand the procedure. By some estimates, more than 50% of the subjects suffering from valve stenosis who are older than 80 years cannot be operated on for valve replacement.

Because of the drawbacks associated with conventional open-heart surgery, percutaneous and minimally-invasive surgical approaches are garnering intense attention. In one technique, a prosthetic valve is configured to be implanted in a much less invasive procedure by way of catheterization. For instance, U.S. Pat. Nos. 5,411,522 and 6,730,118, which are incorporated herein by reference, describe collapsible transcatheter heart valves that can be percutaneously introduced in a compressed state on a catheter and expanded in the desired position by balloon inflation or by utilization of a self-expanding frame or stent.

An important design parameter of a transcatheter heart valve is the diameter of the folded or crimped profile. The diameter of the crimped profile is important because it directly influences the physician's ability to advance the transcatheter heart valve through the femoral artery or vein. More particularly, a smaller profile allows for treatment of a wider population of patients, with enhanced safety.

SUMMARY

The present disclosure is directed toward methods and apparatuses relating to prosthetic valves, such as heart valves, delivery apparatuses, and assemblies of heart valves mounted on delivery apparatuses.

An exemplary embodiment of an assembly for implanting a prosthetic heart valve in a patient's body comprises a delivery apparatus comprising an elongated shaft and a radially expandable prosthetic heart valve mounted on the shaft in a radially collapsed configuration for delivery into the body. The prosthetic heart valve comprises an annular frame having an inflow end portion and an outflow end portion, and a leaflet structure positioned within the frame. The outer diameter of the inflow end portion of the frame is smaller than the outer diameter of the outflow end portion of the frame. The reduced diameter of the inflow end can be due to a reduce amount of materials positioned within the inflow end portion of the frame. The reduced diameter at the inflow end portion can make room for an outer skirt positioned around the inflow end portion.

In some embodiments, the heart valve can further comprise an outer skirt positioned around an outer surface of the inflow end portion of the frame such that an outer diameter of an inflow end portion of the prosthetic valve, inclusive of the outer skirt, is still less than or equal to an outer diameter of an outflow end portion of the prosthetic valve.

In some embodiments, the leaflet structure can comprise a plurality of leaflets that each comprises opposing side tabs on opposite sides of the leaflet. The side tabs can be secured to the outflow end portion of the frame. Each leaflet can further comprise a free outflow edge portion extending between the side tabs adjacent to the outflow end of the frame and an inflow edge portion extending between the side tabs adjacent to the inflow end of the frame. The inflow edge portion can comprise opposing axial edge portions that extend from the side tabs toward the inflow end in a generally axial direction and an intermediate edge portion that extends between the axial edge portions. The intermediate edge portion can comprise a curved apex portion adjacent to the inflow end of the frame and a pair of oblique portions that extend between the axial edge portions and the apex portion. The oblique portions can have a greater radius of curvature than the apex portion, forming a generally V-shaped leaflet.

In some embodiments, the frame comprises a plurality of angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts. In these embodiments, the leaflet structure comprises a plurality of leaflets each comprising two opposing side tabs, each side tab being paired with an adjacent side tab of an adjacent leaflet to form commissures of the leaflet structure. Each commissure extends radially outwardly through a corresponding commissure window of the frame to a location outside of the frame and is sutured to the side struts of the commissure window. In some of these embodiments, the commissure windows of the frame are depressed radially inwardly relative to the portions of the frame extending between adjacent commissure windows when the prosthetic valve is in the collapsed configuration on the shaft.

In some embodiments, the frame comprises an inflow row of openings at the inflow end portion of the frame, an outflow row of openings at the outflow end portion of the frame, and at least one intermediate row of openings between the inflow row of openings and outflow row of openings. The openings of the inflow row of openings are larger than the openings of the at least one intermediate row of openings.

In some embodiments, portions of the leaflet structure protrude through openings in the frame while in the collapsed configuration on the shaft.

In some embodiments, the inflow end portion of the frame comprises a frame thickness that is less than a frame thickness of an intermediate portion of the frame between the inflow end portion and the outflow end portion.

Embodiments disclosed here can comprise an implantable prosthetic valve that is radially collapsible to a collapsed configuration and radially expandable to an expanded configuration. Such prosthetic valves can comprise an annular frame, a leaflet structure positioned within the frame, and an annular outer skirt positioned around an outer surface of the frame. The outer skirt can comprise an inflow edge secured to the frame at a first location, an outflow edge secured to the frame at a second location, and an intermediate portion between the inflow edge and the outflow edge. When the valve is in the expanded configuration, the intermediate portion of the outer skirt comprises slack in the axial direction between the inflow edge of the outer skirt and the outflow edge of the outer skirt, and when the valve is collapsed to the collapsed configuration, the axial distance between the inflow edge of the outer skirt and the outflow edge of the outer skirt increases, reducing the slack in the outer skirt in the axial direction.

In some of these embodiments, the outer skirt is not stretched in the axial direction when the valve is radially collapsed to the collapsed configuration and slack is removed from the intermediate portion of the outer skirt.

Some embodiments of an implantable prosthetic valve comprise an annular frame comprising a plurality of leaflet attachment portions, and a leaflet structure positioned within the frame and secured to the leaflet attachment portions of the frame. The leaflet structure comprises a plurality of leaflets, each leaflet comprising a body portion, two opposing primary side tabs extending from opposite sides of the body portion, and two opposing secondary tabs extending from the body adjacent to the primary side tabs. The secondary tabs are folded about a radially extending crease such that a first portion of the secondary tabs lies flat against the body portion of the respective leaflet, and the secondary tabs are folded about an axially extending crease such that a second portion of the secondary tabs extends in a different plane than the first portion. The second portion of each secondary tab is sutured to a respective primary tab and the secondary tabs are positioned inside of the frame.

In some of these embodiments, the first portion of each the secondary tab pivots about the axially extending crease and lays flat against the second portion of the secondary tab when the valve is collapsed to a radially collapsed configuration. The first portion of each secondary tab comprises an inner edge spaced radially from an inner surface of the frame, and the body portion of the leaflet articulates about the inner edges of the two secondary tabs of the leaflet in response to blood flowing through the valve when the valve is in operation within a patient's body.

Some embodiments disclosed herein comprise an implantable prosthetic valve that is radially collapsible to a collapsed configuration and radially expandable to an expanded configuration. The prosthetic valve comprises an annular frame having an inflow end portion and an outflow end portion, a leaflet structure positioned within the frame, and an annular inner skirt positioned within the frame. The inner skirt is secured to the inside of the frame and the inner skirt comprises a weave of a first set of strands with a second set of strands, both the first and second sets of strands being non-parallel with the axial direction of the valve. When the valve is collapsed from the expanded configuration to the collapsed configuration, the axial length of the frame increases and the both the first and second sets of strands rotate toward the axial direction of the valve, allowing the inner skirt to elongate in the axial direction along with the frame.

In some of these embodiments, the first set of strands are substantially perpendicular to the second set of strands when the valve is in the expanded configuration. In some embodiments, the first set of strands forms a first angle with the axial direction of the valve and the second set of strands forms a second angle with the axial direction of the valve, the first and second angles being substantially equal. In some of these embodiments, the first and second sets of strands comprise 20-denier yarn.

Some embodiments of an implantable prosthetic valve comprise a radially collapsible and expandable annular frame comprising a plurality of angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts. The valve also comprises a leaflet structure positioned within the frame and comprising a plurality of leaflets each comprising two opposing side tabs. Each side tab is paired with an adjacent side tab of an adjacent leaflet to form commissures of the leaflet structure. Each pair of side tabs extends radially outwardly through a corresponding commissure window to a location outside of the frame, the portions of the tabs located outside of the frame extending circumferentially away from one another and along an exterior surface of the side struts. The valve further comprises a plurality of wedges, each wedge being positioned between the side struts of a commissure window and separating the pair of side tabs extending through the commissure window, the wedge being urged radially inwardly against the side tabs.

The wedges can be elongated in an axial direction and correspond in axial length with an axial length of the side struts of the commissure windows. The wedges can further restrict rotational movement of the pair of side tabs relative to the commissure window. Each wedge can be sutured to a flexible reinforcing sheet that is also sutured to each of the pair of side tabs, and each can be sutured to the pair of side tabs. The wedges can comprise a non-metallic material, such as suture material.

The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1-3** show an exemplary embodiment of a prosthetic heart valve.

FIGS. **4-10** show an exemplary frame of the heart valve of FIG. **1**.

FIGS. **11-15**B show another exemplary frame for use in a prosthetic heart valve.

FIGS. **16**A and **16**B show an exemplary inner skirt of the heart valve of FIG. **1**.

FIG. **17** shows another embodiment of a prosthetic heart valve in a compressed (crimped) condition with a deformed frame.

FIG. **18** shows the heart valve of FIG. **1** in a compressed state and mounted on an exemplary balloon catheter.

FIGS. **19-20** show the assembly of the inner skirt of FIG. **16**A with the frame of FIG. **4**.

FIGS. **21-28** show the assembly of an exemplary leaflet structure.

FIGS. **29-35** show the assembly of commissure portions of the leaflet structure with window frame portions of the frame.

FIGS. **36-40** show the assembly of the leaflet structure with the inner skirt along a lower edge of the leaflets.

FIG. **41** shows an exemplary outer skirt laid out flat.

FIGS. **42** and **43** show the exemplary prosthetic heart valve of FIG. **1**.

FIGS. **44-48** show an alternative embodiment of a prosthetic heart valve.

FIGS. **49-52** show portions of an alternative embodiment of a frame.

FIG. **53** shows a portion of the frame of FIG. **4** in a radially compressed state.

FIG. **54** shows a cross-sectional profile of the frame of FIG. **4**, showings a general tapering from the outflow end to the inflow end.

FIG. **55** shows the frame of FIG. **4** in an unrolled, flat configuration.

FIG. **56** shows the heart valve of FIG. **1** in a compressed state and mounted on an exemplary balloon catheter.

FIGS. **57** and **58** shows an embodiment of a leaflet have a generally V-shaped configuration.

FIG. **59** shows a cross-sectional view of an alternative embodiment of a prosthetic valve having a variable thickness frame.

FIG. **60** is a side view of an embodiment of a frame of a valve having commissure windows, prior to mounting a leaflet structure to the frame.

FIG. **60**A is an enlarged side view of one commissure window of FIG. **60**.

FIG. **61** is a perspective view of an embodiment of a prosthetic valve comprising the frame of FIG. **60** and a leaflet structure mounted to the valve.

FIG. **62** is an enlarged side view of one commissure of the valve of FIG. **61**.

FIGS. **63-71** are cross-sectional views of a commissure of the valve of FIG. **61** showing various techniques for suturing a pair of leaflet side tabs to a commissure window using a reinforcing sheet.

FIGS. **72-74** show balloon expansion of an alternative embodiment of a frame for a prosthetic valve having inflow and outflow end portions of reduced thickness.

DETAILED DESCRIPTION

FIGS. **1-3** show various views of a prosthetic heart valve **10**, according to one embodiment. The illustrated valve is adapted to be implanted in the native aortic annulus, although in other embodiments it can be adapted to be implanted in the other native annuluses of the heart. The valve **10** can have four main components: a stent, or frame, **12**, a valvular structure **14**, an inner skirt **16**, and an outer skirt **18**.

The valvular structure **14** can comprise three leaflets **40**, collectively forming a leaflet structure, which can be arranged to collapse in a tricuspid arrangement, as best shown in FIG. **2**. The lower edge of leaflet structure **14** desirably has an undulating, curved scalloped shape (suture line **154** shown in FIG. **1** tracks the scalloped shape of the leaflet structure). By forming the leaflets with this scalloped geometry, stresses on the leaflets are reduced, which in turn improves durability of the valve. Moreover, by virtue of the scalloped shape, folds and ripples at the belly of each leaflet (the central region of each leaflet), which can cause early calcification in those areas, can be eliminated or at least minimized. The scalloped geometry also reduces the amount of tissue material used to form leaflet structure, thereby allowing a smaller, more even crimped profile at the inflow end of the valve. The leaflets **40** can be formed of pericardial tissue (e.g., bovine pericardial tissue), biocompatible synthetic materials, or various other suitable natural or synthetic materials as known in the art and described in U.S. Pat. No. 6,730,118, which is incorporated by reference herein.

The bare frame **12** is shown in FIG. **4**. The frame **12** can be formed with a plurality of circumferentially spaced slots, or commissure windows, **20** (three in the illustrated embodiment) that are adapted to mount the commissures of the valvular structure **14** to the frame, as described in greater detail below. The frame **12** can be made of any of various suitable plastically-expandable materials (e.g., stainless steel, etc.) or self-expanding materials (e.g., Nitinol) as known in the art. When constructed of a plastically-expandable material, the frame **12** (and thus the valve **10**) can be crimped to a radially compressed state on a delivery catheter and then expanded inside a patient by an inflatable balloon or equivalent expansion mechanism. When constructed of a self-expandable material, the frame **12** (and thus the valve **10**) can be crimped to a radially compressed state and restrained in the compressed state by insertion into a sheath or equivalent mechanism of a delivery catheter. Once inside the body, the valve can be advanced from the delivery sheath, which allows the valve to expand to its functional size.

Suitable plastically-expandable materials that can be used to form the frame **12** include, without limitation, stainless steel, a nickel based alloy (e.g., a cobalt-chromium or a nickel-cobalt-chromium alloy), polymers, or combinations thereof. In particular embodiments, frame **12** is made of a nickel-cobalt-chromium-molybdenum alloy, such as MP35N™ (tradename of SPS Technologies), which is equivalent to UNS R30035 (covered by ASTM F562-02). MP35N™/UNS R30035 comprises 35% nickel, 35% cobalt, 20% chromium, and 10% molybdenum, by weight. It has been found that the use of MP35N to form frame **12** provides superior structural results over stainless steel. In particular, when MP35N is used as the frame material, less material is needed to achieve the same or better performance in radial and crush force resistance, fatigue resistances, and corrosion resistance. Moreover, since less material is required, the crimped profile of the frame can be reduced, thereby providing a lower profile valve assembly for percutaneous delivery to the treatment location in the body.

Referring to FIGS. **4** and **5**, the frame **12** in the illustrated embodiment comprises a first, lower row I of angled struts **22** arranged end-to-end and extending circumferentially at the inflow end of the frame; a second row II of circumferentially extending, angled struts **24**; a third row III of circumferentially extending, angled struts **26**; a fourth row IV of circumferentially extending, angled struts **28**; and a fifth row V of circumferentially extending, angled struts **32** at the outflow end of the frame. A plurality of substantially straight axially extending struts **34** can be used to interconnect the struts **22** of the first row I with the struts **24** of the second row II. The fifth row V of angled struts **32** are connected to the fourth row IV of angled struts **28** by a plurality of axially extending window frame portions **30** (which define the commissure windows **20**) and a plurality of axially extending struts **31**. Each axial strut **31** and each frame portion **30** extends from a location defined by the convergence of the lower ends of two angled struts **32** to another location defined by the convergence of the upper

ends of two angled struts **28**. FIGS. **6**, **7**, **8**, **9** and **10** are enlarged views of the portions of the frame **12** identified by letters A, B, C, D and E, respectively, in FIG. **4**.

Each commissure window frame portion **30** mounts a respective commissure of the leaflet structure **14**. As can be seen each frame portion **30** is secured at its upper and lower ends to the adjacent rows of struts to provide a robust configuration that enhances fatigue resistance under cyclic loading of the valve compared to known cantilevered struts for supporting the commissures of the leaflet structure. This configuration enables a reduction in the frame wall thickness to achieve a smaller crimped diameter of the valve. In particular embodiments, the thickness T of the frame **12** (FIG. **4**) measured between the inner diameter and outer diameter is about 0.48 mm or less.

The struts and frame portions of the frame collectively define a plurality of open cells of the frame. At the inflow end of the frame **12**, struts **22**, struts **24**, and struts **34** define a lower row of cells defining openings **36**. The second, third, and fourth rows of struts **24**, **26**, and **28** define two intermediate rows of cells defining openings **38**. The fourth and fifth rows of struts **28** and **32**, along with frame portions **30** and struts **31**, define an upper row of cells defining openings **40**. The openings **40** are relatively large and are sized to allow portions of the leaflet structure **14** to protrude, or bulge, into and/or through the openings **40** when the frame **12** is crimped in order to minimize the crimping profile.

As best shown in FIG. **7**, the lower end of the strut **31** is connected to two struts **28** at a node or junction **44**, and the upper end of the strut **31** is connected to two struts **32** at a node or junction **46**. The strut **31** can have a thickness S1 that is less than the thicknesses S2 of the junctions **44**, **46**. FIG. **53** shows a portion of the frame **12** in a crimped state. The junctions **44**, **46**, along with junctions **64**, prevent full closure of openings **40**. FIG. **18** shows the valve **10** crimped on a balloon catheter. As can be seen, the geometry of the struts **31**, and junctions **44**, **46** and **64** assists in creating enough space in openings **40** in the crimped state to allow portions of the leaflets to protrude (i.e., bulge) outwardly through openings. This allows the valve to be crimped to a relatively smaller diameter than if all of the leaflet material is constrained within the crimped frame.

The frame **12** is configured to prevent or at least minimize possible over-expansion of the valve at a predetermined balloon pressure, especially at the outflow end portion of the frame, which supports the leaflet structure **14**. In one aspect, the frame is configured to have relatively larger angles **42***a*, **42***b*, **42***c*, **42***d*, **42***e* between struts. The larger the angle, the greater the force required to open (expand) the frame. This phenomenon is schematically illustrated in FIGS. **15**A and **15**B. FIG. **15**A shows a strut **32** when the frame **12** is in its compressed state (e.g., mounted on a balloon). The vertical distance d_1 between the ends of the struts is greatest when the frame is compressed, providing a relatively large moment between forces F_1 and F_2 acting on the ends of the strut in opposite directions upon application of an opening force from inflation of the balloon (or expansion of another expansion device). When the frame expands radially, the vertical distance between the ends of the strut decreases to a distance d_2, as depicted in FIG. **15**B. As the vertical distance decreases, so does the moment between forces F_1 and F_2. Hence, it can be seen that a relatively greater expansion force is required as the vertical distance and the moment between the ends of the strut decreases. Moreover, strain hardening (stiffening) at the ends of the strut increases as the frame expands, which increases the expansion force required to induce further plastic deformation at the ends of the strut. As such, the angles between the struts of the frame can be selected to limit radial expansion of the frame at a given opening pressure (e.g., inflation pressure of the balloon). In particular embodiments, these angles are at least 110 degrees or greater when the frame is expanded to its functional size, and even more particularly these angles are at least 120 degrees or greater when the frame is expanded to its functional size.

In addition, the inflow and outflow ends of a frame generally tend to over-expand more so than the middle portion of the frame due to the "dog boning" effect of the balloon used to expand the valve. To protect against over-expansion of the leaflet structure **14**, the leaflet structure desirably is secured to the frame **12** below the upper row of struts **32**, as best shown in FIG. **1**. FIG. **55** shows a flattened view of the frame **12** similar to FIG. **5**, but showing a line **176** superimposed over the frame to indicate the position of the upper edges of the leaflets **40**. Thus, in the event that the outflow end of the frame is over-expanded, the leaflet structure is positioned at a level below where over-expansion is likely to occur, thereby protecting the leaflet structure from over-expansion.

In a known valve construction, the leaflets can protrude outwardly beyond the outflow end of the frame when the valve is crimped if the leaflets are mounted too close to the distal end of the frame. If the delivery catheter on which the crimped valve is mounted includes a pushing mechanism or stop member that pushes against or abuts the outflow end of the valve (for example, to maintain the position of the crimped valve on the delivery catheter), the pushing member or stop member can damage the exposed leaflets that extend beyond the outflow end of the frame. Another benefit of mounting the leaflets at a location spaced from the outflow end **178** of the frame is that when the valve is crimped on a delivery catheter, as shown in FIG. **56**, the leaflets **40** do not protrude beyond the outflow end **178** of the frame in the axial direction. As such, if the delivery catheter includes a pushing mechanism or stop member that pushes against or abuts the outflow end of the valve, the pushing mechanism or stop member can contact the end **178** of the frame, and not leaflets **40**, so as to avoid damage to the leaflets.

Also, as can be seen in FIG. **5**, the openings **36** of the lowermost row of openings in the frame are relatively larger than the openings **38** of the two intermediate rows of openings. As shown in FIG. **54**, this allows the frame, when crimped, to assume an overall tapered shape that tapers from a maximum diameter D_1 at the outflow end of the valve to a minimum diameter D_2 at the inflow end of the valve. When crimped, the frame **12** has a reduced diameter region extending along a portion of the frame adjacent the inflow end of the frame, indicated by reference number **174**, that generally corresponds to the region of the frame covered by the outer skirt **18**. The diameter of region **174** is reduced compared to the diameter of the upper portion of the frame (which is not covered by the outer skirt) such that the outer skirt **18** does not increase the overall crimp profile of the valve. When the valve is deployed, the frame can expand to the cylindrical shape shown in FIG. **4**. In one example, the frame of a 26-mm valve, when crimped, had a diameter D_1 of 14 French at the outflow end of the valve and a diameter D_2 of 12 French at the inflow end of the valve.

FIGS. **11** and **12** show an alternative frame **50** that can be incorporated in the valve **10**. The frame **50** comprises multiple rows of circumferentially extending, angled struts **52** that are connected to each other at nodes, or connecting portions, **54** and **56**. The uppermost row of struts **52** are connected to an adjacent row of struts by a plurality of axially extending struts **58** and commissure window frame portions **60**. Each commissure frame portion **60** defines a slot, or

commissure window, **62** for mounting a respective commissure of the valvular structure, as described in greater detail below. In particular embodiments, the thickness T of the frame **50** is about 0.45 mm or less. FIGS. **13** and **14** are enlarged views of the portions of the frame **50** identified by letters A and B, respectively, in FIG. **12**.

The main functions of the inner skirt **16** are to assist in securing the valvular structure **14** to the frame **12** and to assist in forming a good seal between the valve and the native annulus by blocking the flow of blood through the open cells of the frame **12** below the lower edge of the leaflets. The inner skirt **16** desirably comprises a tough, tear resistant material such as polyethylene terephthalate (PET), although various other synthetic or natural materials can be used. The thickness of the skirt desirably is less than 6 mil, and desirably less than 4 mil, and even more desirably about 2 mil. In particular embodiments, the skirt **16** can have a variable thickness, for example, the skirt can be thicker at its edges than at its center. In one implementation, the skirt **16** can comprise a PET skirt having a thickness of about 0.07 mm at its edges and about 0.06 mm at its center. The thinner skirt can provide for better crimping performances while still providing good perivalvular sealing.

The skirt **16** can be secured to the inside of frame **12** via sutures **70**, as shown in FIG. **39**. Valvular structure **14** can be attached to the skirt via one or more thin PET reinforcing strips **72** (which collectively can form a sleeve), discussed below, which enables a secure suturing and protects the pericardial tissue of the leaflet structure from tears. Valvular structure **14** can be sandwiched between skirt **16** and the thin PET strips **72** as shown in FIG. **38**. Sutures **154**, which secure the PET strip and the leaflet structure **14** to skirt **16**, can be any suitable suture, such as an Ethibond suture. Sutures **154** desirably track the curvature of the bottom edge of leaflet structure **14**, as described in more detail below.

Known fabric skirts comprise a weave of warp and weft fibers that extend perpendicular to each other and with one set of fibers extending perpendicularly to the upper and lower edges of the skirt. When the metal frame, to which the fabric skirt is secured, is radially compressed, the overall axial length of the frame increases. Unfortunately, a fabric skirt, which inherently has limited elasticity, cannot elongate along with the frame and therefore tends to deform the struts of the frame and prevents uniform crimping.

FIG. **17** shows an example of a crimped valve where the struts have been deformed in several places, as indicated by reference number **100**, by a skirt having fibers that extend perpendicular to the upper and lower edges of the skirt. Moreover, the fabric tends to bunch or create bulges of excess material in certain locations, which limits the minimum crimping profile and prevents uniform crimping.

Referring to FIG. **16**B, in contrast to known fabric skirts, the skirt **16** desirably is woven from a first set of fibers, or yarns or strands, **78** and a second set of fibers, or yarns or strands, **80**, both of which are non-perpendicular to the upper edge **82** and the lower edge **84** of the skirt. In particular embodiments, the first set of fibers **78** and the second set of fibers **80** extend at angles of about 45 degrees relative to the upper and lower edges **82**, **84**. The skirt **16** can be formed by weaving the fibers at 45 degree angles relative to the upper and lower edges of the fabric. Alternatively, the skirt can be diagonally cut from a vertically woven fabric (where the fibers extend perpendicular to the edges of the material) such that the fibers extend at 45 degree angles relative to the cut upper and lower edges of the skirt. As further shown in FIG. **16**B, the opposing short edges **86**, **88** of the skirt desirably are non-perpendicular to the upper and lower edges **82**, **84**. For example, the short edges **86**, **88** desirably extend at angles of about 45 degrees relative to the upper and lower edges and therefore are aligned with the first set of fibers **78**. Therefore the overall shape of the skirt is that of a rhomboid.

FIGS. **19**A and **19**B shows the skirt **16** after opposing edge portions **90**, **92** have been sewn together to form the annular shape of the skirt. As shown, the edge portion **90** can be placed in an overlapping relationship relative to the opposite edge portion **92**, and the two edge portions can be sewn together with a diagonally extending suture line **94** that is parallel to edges **86**, **88**. The upper edge portion of the skirt **16** can be formed with a plurality of projections **96** that define an undulated shape that generally follows the shape of the fourth row of struts **28** immediately adjacent the lower ends of axial struts **31**. In this manner, as best shown in FIG. **20**, the upper edge of skirt **16** can be tightly secured to struts **28** with sutures **70**. Skirt **16** can also be formed with slits **98** to facilitate attachment of the skirt to the frame. Slits **98** are dimensioned so as to allow an upper edge portion of skirt to be partially wrapped around struts **28** and reduce stresses in the skirt during the attachment procedure. For example, in the illustrated embodiment, skirt **16** is placed on the inside of frame **12** and an upper edge portion of the skirt is wrapped around the upper surfaces of struts **28** and secured in place with sutures **70**. Wrapping the upper edge portion of the skirt around struts **28** in this manner provides for a stronger and more durable attachment of the skirt to the frame. The skirt **16** can also be secured to the first, second, and third rows of struts **22**, **24**, and **26**, respectively, with sutures **70**.

Referring again to FIG. **16**B, due to the orientation of the fibers relative to the upper and lower edges, the skirt can undergo greater elongation in the axial direction (i.e., in a direction from the upper edge **82** to the lower edge **84**).

Thus, when the metal frame **12** is crimped (as shown in FIG. **18**), the skirt **16** can elongate in the axial direction along with the frame and therefore provides a more uniform and predictable crimping profile. Each cell of the metal frame in the illustrated embodiment includes at least four angled struts that rotate towards the axial direction (i.e., the angled struts become more aligned with the length of the frame). The angled struts of each cell function as a mechanism for rotating the fibers of the skirt in the same direction of the struts, allowing the skirt to elongate along the length of the struts. This allows for greater elongation of the skirt and avoids undesirable deformation of the struts when the valve is crimped.

In addition, the spacing between the woven fibers or yarns can be increased to facilitate elongation of the skirt in the axial direction. For example, for a PET skirt **16** formed from 20-denier yarn, the yarn density can be about 15% to about 30% less than a conventional PET skirt. In some examples, the yarn spacing of the skirt **16** can be from about 155 yarns per inch to about 180 yarns per inch, such about 160 yarns per inch, whereas in a conventional PET skirt the yarn spacing can be from about 217 yarns per inch to about 247 yarns per inch. The oblique edges **86**, **88** promote uniform and even distribution of the fabric material along inner circumference of the frame during crimping so as to minimize bunching of the fabric to facilitate uniform crimping to the smallest possible diameter. Additionally, cutting diagonal sutures in a vertical manner may leave loose fringes along the cut edges. The oblique edges **86**, **88** help minimize this from occurring. As noted above, FIG. **17** shows a crimped valve with a conventional skirt that has fibers that run perpendicular to the upper and lower edges of the skirt. Comparing FIGS. **17** and **18**, it is apparent that the construction of skirt **16** avoids

undesirable deformation of the frame struts and provides more uniform crimping of the frame.

In alternative embodiments, the skirt can be formed from woven elastic fibers that can stretch in the axial direction during crimping of the valve. The warp and weft fibers can run perpendicular and parallel to the upper and lower edges of the skirt, or alternatively, they can extend at angles between 0 and 90 degrees relative to the upper and lower edges of the skirt, as described above.

The inner skirt **16** can be sutured to the frame **12** at locations away from the suture line **154** so that the skirt can be more pliable in that area (see FIG. **28**). This can avoid stress concentrations at the suture line **154**, which attaches the lower edges of the leaflets to the skirt **16**.

As noted above, the leaflet structure **14** in the illustrated embodiment includes three flexible leaflets **40** (although a greater or fewer number of leaflets can be used). As best shown in FIG. **21**, each leaflet **40** in the illustrated configuration has an upper (outflow) free edge **110** extending between opposing upper tabs **112** on opposite sides of the leaflet. Below each upper tab **112** there is a notch **114** separating the upper tab from a corresponding lower tab **116**. The lower (inflow) edge portion **108** of the leaflet extending between respective ends of the lower tabs **116** includes vertical, or axial, edge portions **118** on opposites of the leaflets extending downwardly from corresponding lower tabs **116** and a substantially V-shaped, intermediate edge portion **120** having a smooth, curved apex portion **119** at the lower end of the leaflet and a pair of oblique portions **121** that extend between the axial edge portions and the apex portion. The oblique portions can have a greater radius of curvature than the apex portion. Each leaflet **40** can have a reinforcing strip **72** secured (e.g., sewn) to the inner surface of the lower edge portion **108**, as shown in FIG. **22**.

The leaflets **40** can be secured to one another at their adjacent sides to form commissures **122** of the leaflet structure. A plurality of flexible connectors **124** (one of which is shown in FIG. **23**) can be used to interconnect pairs of adjacent sides of the leaflets and to mount the leaflets to the commissure window frame portions **30**. The flexible connectors **124** can be made from a piece of woven PET fabric, although other synthetic and/or natural materials can be used. Each flexible connector **124** can include a wedge **126** extending from the lower edge to the upper edge at the center of the connector. The wedge **126** can comprise a non-metallic material, such as a rope or a piece of Ethibond 2-0 suture material, secured to the connector with a temporary suture **128**. The wedge **126** helps prevent rotational movement of the leaflet tabs once they are secured to the commissure window frame portions **30**. The connector **124** can have a series of inner notches **130** and outer notches **132** formed along its upper and lower edges.

FIG. **24** shows the adjacent sides of two leaflets **40** interconnected by a flexible connector **124**. The opposite end portions of the flexible connector **124** can be placed in an overlapping relationship with the lower tabs **116** with the inner notches **130** aligned with the vertical edges of the tabs **116**. Each tab **116** can be secured to a corresponding end portion of the flexible connector **124** by suturing along a line extending from an outer notch **132** on the lower edge to an outer notch **132** on the upper edge of the connector. Three leaflets **40** can be secured to each other side-to-side using three flexible connectors **124**, as shown in FIG. **25**.

Referring now to FIGS. **26** and **27**, the adjacent sub-commissure portions **118** of two leaflets can be sutured directly to each other. In the example shown, PTFE-6-0 suture material is used to form in-and-out stitches **133** and comb stitches **134** that extend through the sub-commissure portions **118** and the reinforcing strips **72** on both leaflets. The two remaining pairs of adjacent sub-commissure portions **118** can be sutured together in the same manner to form the assembled leaflet structure **14**, which can then be secured to the frame **12** in the following manner.

As noted above, the inner skirt **16** can be used to assist in suturing the leaflet structure **14** to the frame. As shown in FIG. **28**, the skirt **16** can have an undulating temporary marking suture **136** to guide the attachment of the lower edges of each leaflet **40**. The skirt **16** itself can be sutured to the struts of the frame **12** using sutures **70**, as noted above, before securing the leaflet structure **14** to the skirt **16**. The struts that intersect the marking suture **136** desirably are not attached to the skirt **16**. This allows the skirt **16** to be more pliable in the areas not secured to the frame and minimizes stress concentrations along the suture line that secures the lower edges of the leaflets to the skirt. The portion of the skirt **16** demarcated by rectangle **140** initially is left unsecured to the frame **12**, and is later secured to the frame after the leaflet structure **14** is secured to the skirt, as further described below. As noted above, when the skirt is secured to the frame, the fibers **78**, **80** of the skirt (see FIG. **16**B) generally align with the angled struts of the frame to promote uniform crimping and expansion of the frame.

FIG. **29** is a cross-sectional view of a portion of the frame and leaflet structure showing the adjacent tab portions of two leaflets secured to a corresponding window frame portion **30**. FIGS. **30**-**36** show one specific approach for securing the commissure portions **122** of the leaflet structure **14** to the commissure window frame portions **30** of the frame. First, as shown in FIG. **30**, the flexible connector **124** securing two adjacent sides of two leaflets is folded widthwise and the upper tab portions **112** are folded downwardly against the flexible connector. As best shown in FIGS. **30** and **31**, each upper tab portion **112** is creased lengthwise (vertically) to assume an L-shape having an inner portion **142** folded against the inner surface of the leaflet and an outer portion **144** folded against the connector **124**. The outer portion **144** can then be sutured to the connector **124** along a suture line **146**. Next, as shown in FIG. **31**, the commissure tab assembly (comprised of a pair of lower tab portions **116** connected by connector **124**) is inserted through the commissure window **20** of a corresponding window frame portion **30**. FIG. **32** is a side view of the frame **12** showing the commissure tab assembly extending outwardly through the window frame portion **30**.

As best shown in FIGS. **29** and **33**, the commissure tab assembly is pressed radially inwardly at the wedge **126** such that one of the lower tab portions **116** and a portion of the connector **124** is folded against the frame **12** on one side of the window frame portion **30** and the other lower tab portion **116** and a portion of the connector **124** is folded against the frame **12** on other side of the window frame portion **30**. A pair of suture lines **148** are formed to retain the lower tab portions **116** against the frame **12** in the manner shown in FIG. **29**. Each suture line **148** extends through connector **124**, a lower tab portion **116**, the wedge **126**, and another portion of connector **124**. Then, as shown in FIGS. **29** and **34**, each lower tab portion **116** is secured to a corresponding upper tab portion **112** with a primary suture line **150** that extends through one layer of connector **124**, the lower tab portion **116**, another layer of connector **124**, another layer of connector **124**, and the upper tab portion **112**. Finally, as shown in FIGS. **29** and **35**, the suture material used to form the primary suture line **150** can be used to further form whip stitches **152** at the edges of the tab portions **112**, **116** that extend through two layers of connector **124** sandwiched between tab portions **112**, **116**.

As shown in FIGS. **29** and **30**, the folded down upper tab portions **112** form a double layer of leaflet material at the commissures. The inner portions **142** of the upper tab portions **112** are positioned flat abutting layers of the two leaflets **40** forming the commissures, such that each commissure comprises four layers of leaflet material just inside of the window frames **30**. This four layered portion of the commissures can be more resistant to bending, or articulating, than the portion of the leaflets **40** just radially inward from the relatively more rigid four layered portion. This causes the leaflets **40** to articulate primarily at inner edges **143** of the folded-down inner portions **142** in response to blood flowing through the valve during operation within the body, as opposed to articulating about the axial struts of the window frames **30**. Because the leaflets articulate at a location spaced radially inwardly from the window frames **30**, the leaflets can avoid contact with and damage from the frame. However, under high forces, the four layered portion of the commissures can splay apart about a longitudinal axis **145** (FIG. **29**) adjacent to the window frame **30**, with each inner portion **142** folding out against the respective outer portion **144**. For example, this can occur when the valve **10** is compressed and mounted onto a delivery shaft, allowing for a smaller crimped diameter. The four layered portion of the commissures can also splay apart about axis **145** when the balloon catheter is inflated during expansion of the valve, which can relieve some of the pressure on the commissures caused by the balloon and so the commissures are not damaged during expansion.

After all three commissure tab assemblies are secured to respective window frame portions **30**, the lower edges of the leaflets **40** between the commissure tab assemblies can be sutured to the inner skirt **16**. For example, as shown in FIGS. **36-38**, each leaflet **40** can be sutured to the skirt **16** along suture line **154** using, for example, Ethibond thread. The sutures can be in-and-out sutures extending through each leaflet **40**, the skirt **16** and each reinforcing strip **72**. Each leaflet **40** and respective reinforcing strip **72** can be sewn separately to the skirt **16**. In this manner, the lower edges of the leaflets are secured to the frame **12** via the skirt **16**. As shown in FIG. **38**, the leaflets can be further secured to the skirt with blanket sutures **156** that extend through each reinforcing strip **72**, leaflet **40** and the skirt **16** while looping around the edges of the reinforcing strips **72** and leaflets **40**. The sutures **156** can be formed from PTFE suture material. FIGS. **39** and **40** show the frame **12**, leaflet structure **14** and the skirt **16** after securing the leaflet structure and the skirt to the frame and the leaflet structure to the skirt.

FIG. **41** shows a flattened view of the outer skirt **18** prior to its attachment to the frame **12**. The outer skirt **18** can be laser cut or otherwise formed from a strong, durable piece of material, such as woven PET, although other synthetic or natural materials can be used. The outer skirt **18** can have a substantially straight lower edge **160** and an upper edge **162** defining a plurality of alternating projections **164** and notches **166**. As best shown in FIG. **42**, the lower edge **160** of the skirt **18** can be sutured to the lower edge of the inner skirt **16** at the inflow end of the valve. As shown in FIG. **43**, each projection **164** can be sutured to the second rung II of struts **24** of the frame **12**. The corners **162** of the projections **164** can be folded over respective struts of rung II and secured with sutures **168**.

As can be seen in FIGS. **1**, **3** and **43**, the outer skirt **18** is secured to the frame **12** such that when the frame is in its expanded state, there is excess material or slack between the outer skirt's lower and upper edges **160**, **162** that does not lie flat against the outer surface of the frame **12**. In other words, the outer skirt is configured with excess material which causes the outer skirt to bulge outwardly as the frame foreshortens (i.e., shortens in length) during radial expansion. Accordingly, when the valve **10** is deployed within the body, the excess material of the outer skirt **18** can fill in gaps between the frame **12** and the surrounding native annulus to assist in forming a good fluid-tight seal between the valve and the native annulus. The outer skirt **18** therefore cooperates with the inner skirt **16** to avoid perivalvular leakage after implantation of the valve **10**. In another advantageous feature, the slack between the lower and upper edges of the outer skirt **18** allows the frame **12** to elongate axially during crimping without any resistance from the outer skirt and the outer skirt does not substantially affect the outer diameter of the prosthetic valve in the crimped condition.

FIG. **56** shows the valve **10** of FIGS. **1-3** and **42-43** mounted on an elongated shaft **180** of a delivery apparatus, forming a delivery assembly for implanting the valve **10** in a patient's body. The valve **10** is mounted in a radially collapsed configuration for delivery into the body. The shaft **180** comprises an inflatable balloon **182** for expanding the balloon within the body, the crimped valve **10** being positioned over the deflated balloon. The frame **12** of the valve **10**, when in the radially compressed, mounted configuration, comprises an inflow end portion **174** (see FIG. **54**) that has an outer diameter D_2 that is smaller than the outer diameter D_1 of the outflow end portion of the frame. The tapering of the frame can be at least partially due to the V-shaped leaflets **40**, as the V-shaped leaflets have less leaflet material within the inflow end portion of the frame **12** compared to a more rounded, U-shaped leaflet. Due to the tapered shape of the frame **12** in the mounted state, even with the additional thickness of the outer skirt **18** positioned around the inflow end portion **174** of the frame **12** the overall outer diameter of the inflow end portion of the valve **10** can be about equal to, or less than, the overall outer diameter of the outflow end portion of the valve.

Furthermore, as shown in FIG. **56**, the valve **10** comprises commissure portions of the leaflets extending radially outwardly through corresponding window frame portion **30** to locations outside of the frame and sutured to the side struts of the commissure window frame. To minimize the crimp profile of the valve, the window frame portions **30** can be depressed radially inwardly relative to the surrounding portions of the frame, such as the frame portions extending between adjacent commissure windows, when the valve is radially compressed to the collapsed configuration on the shaft. For example, the commissure windows **30** of the frame can be depressed inwardly a radial distance of between 0.2 mm and 1.0 mm relative to the portions of the frame extending between adjacent commissure windows when the valve is radially collapsed. In this way, the outer diameter of the outflow end portion the valve comprising the commissure portions can be generally consistent, as opposed to the commissure portions jutting outward from the surrounding portions of the valve, which could hinder delivery of the valve into the body. Even with the radially depressed commissure window frames **30**, the outer diameter of the inflow end portion of the frame can still be smaller than, or about equal to, the outer diameter of the outflow end portion of the frame when the valve is radially collapsed on the shaft, allowing for a minimal maximum overall diameter of the valve. By minimizing the diameter of the valve when mounted on the delivery shaft, the assembly can contained within a smaller diameter catheter and thus can be passed through smaller vessels in the body and can be less invasive in general.

FIG. **44** illustrates a prosthetic heart valve **200**, according to another embodiment. The heart valve **200** includes a frame, or stent, **202** and a leaflet structure **204** mounted on the stent.

The leaflet structure **204** can include a plurality of leaflets **218** (e.g., three, as depicted), which can be sutured to each other and to the frame **202** using suitable techniques and/or mechanisms. The frame **202** can be adapted to include commissure frame portions **30** (as shown in FIG. **4**) to assist in suturing the leaflets to the frame.

The frame **202** shares some design features of the frame **12** described above. In particular, like frame **12**, the frame **202** has relatively large frame openings **206** along the area of the frame that supports the leaflet structure, as shown in FIG. **45**. The openings **206** are defined by a row of angled struts **208** at the outflow end of the frame, a plurality of axially extending, circumferentially spaced struts **210**, and an intermediate row of angled struts **212**. As shown, the axial struts **210** desirably are thinner than the junctions **214** connecting the opposite ends of the axial struts **210** to the convergence of two struts **212** and to the convergence of two struts **208**. By virtue of this configuration, the width of openings **206** remain large enough when the valve is radially compressed to a delivery configuration to allow portions of the leaflet structure **204** to protrude outwardly through the openings, as indicated at **216** in FIGS. **46** and **47**. This allows the valve to be crimped to a relatively smaller diameter than if all of the leaflet material is constrained within the crimped frame.

For purposes of comparison, FIG. **48** is a cross section of a known prosthetic valve **250** showing the valve in its crimped state. When the valve is radially compressed, the spacing between adjacent struts is relatively small and does not allow portions of the leaflet structure to protrude outwardly through the frame. Consequently, the presence of all of the leaflet material being constrained within the inside of the frame limits the crimping diameter of the valve.

FIGS. **49** and **50** show a flattened section of an alternative frame construction that can allow portions of the leaflets to protrude outwardly through the frame in the crimped state. This frame construction can be implemented in the valve **10** described above. FIG. **49** shows the frame section in the radially compressed state while FIG. **50** shows the frame section in the radially expanded state. The frame (only a portion of which is shown) includes a first, circumferentially extending row of angled struts **442** and at least a second, circumferentially extending row of angled struts **444**. Some openings in the frame are diamond shaped openings **446** formed by adjacent struts **442** connected to each other at their upper ends and adjacent struts **444** connected to each other at their lower ends. The frame also includes larger openings **448** that are formed by adjacent struts **442** connected at their upper ends to respective ends of a horizontal strut **450** and by adjacent struts **444** connected at their lower ends to respective ends of a horizontal strut **452**. When the frame is radially compressed, the horizontal struts **450**, **452** maintains the width W of openings **448** large enough to permit portions of the valve's leaflets to protrude outwardly through the frame. Thus, the width of openings **448** is greater than the width of openings **446** when the frame is crimped. The frame can be formed with openings **446**, **448** alternating around the circumference of the frame. Alternatively, openings **448** can be located at selected positions along the frame's length and circumference to correspond to areas where the leaflet material tend to bunch up within the frame, such as between the commissures.

FIGS. **51** and **52** show a flattened section of another frame construction that can allow portions of the leaflets to protrude outwardly through the frame in the crimped state. This frame construction can be implemented in the valve **10** described above. FIG. **51** shows the frame section in the radially compressed state while FIG. **52** shows the frame section in the radially expanded state. The frame (only a portion of which is shown) includes a first, circumferentially extending row of angled struts **402** and at least a second, circumferentially extending row of angled struts **404**. Some openings in the frame are diamond shaped openings **406** formed by adjacent struts **402** connected to each other at their upper ends and adjacent struts **404** connected to each other at their lower ends. The frame also includes openings **408** that are formed by adjacent struts **402** connected at their upper ends to an enlarged node or junction **410** and by adjacent struts **404** connected at their lower ends to an enlarged node or junction **412**. The junctions **410**, **412** add rigidity to the frame at those locations such that when the frame is radially compressed, the width W of openings **408** remains large enough to permit portions of the valve's leaflets to protrude outwardly through the frame. Thus, the width of openings **408** is greater than the width of openings **406** when the frame is crimped. The frame can be formed with openings **406**, **408** alternating around the circumference of the frame. Alternatively, openings **408** can be located at selected positions along the frame's length and circumference to correspond to areas where the leaflet material tend to bunch up within the frame, such as between the commissures.

FIG. **57** shows a leaflet **500** for a prosthetic valve (e.g., valve **10** or **200**), according to another embodiment. The leaflet **500** has an overall V-shape, similar to leaflets **40** described above. The leaflet **500** has two tab portions **502** on opposite sides of the leaflets which are secured to adjacent tab portions of other leaflets to form the commissures of the leaflet structure. The sub-commissure portion of the leaflet **500** (the portion below the tabs **502**) include two substantially straight edges **504** that extend from respective locations just below the tabs **502** to a curved lower edge **506**. FIG. **58** shows the general shape of the leaflet **500** when the valve is crimped. The frame (not shown in FIGS. **57-58**) slightly elongates when crimped, causing the leaflet **500** to become slightly elongated.

The tapered profile of the sub-commissure portion of the leaflet reduces the amount of leaflet material in the lower half of the crimped valve to minimize the crimp diameter of that portion of the valve. Thus, if additional components are mounted to that portion of the valve, such as an outer skirt **18**, the reduced profile of that portion of the valve can help offset or minimize the increase in diameter caused by the additional component. Additionally, the commissure tabs **502** are relatively short and require less sutures for forming the commissures of the leaflet structure than known leaflet designs (such as T-shaped and scalloped leaflets), which better distributes and reduces the bulkiness of the leaflet material when the valve is crimped.

FIG. **59** shows a cross-sectional view of a valve **500**, according to another embodiment. The valve **500** comprises a frame **502**, leaflets **504**, and an outer skirt **18** mounted (e.g., by sutures) to the outer surface of the frame **502**. The frame **502** has a thickness that varies along its length to optimize strength where needed, yet minimize material (and therefore crimp profile) at selected regions of the frame. In the embodiment shown, the outflow end portion **506** of the frame has a maximum thickness T_1 (measured from the inside diameter to the outside diameter of that portion of the frame) and the inflow end portion **508** of the frame has a minimum thickness T_2 (measured from the inside diameter to the outside diameter of that portion of the frame). It should be noted that the struts of the frame **502** (which are not shown in FIG. **59**) that form the outflow end portion **506** have a thickness T_1 and the struts that form the inflow end portion **508** have a thickness T_2. The frame **502** can have an identical construction to the frame **12**

described above, except for the variable thickness of the frame. The areas of reduced thickness can be formed using a variety of manufacturing techniques, such as electro-polishing selected portions of the frame (the non-polished portions can be masked), grinding selected portions of the frame, wire cutting, or other suitable techniques.

The outflow end portion **502** generally corresponds to the region of the frame that supports the commissures of the leaflets **504** and typically experiences the greatest loading on the valve. Therefore the outflow end portion **502** of the frame has a greater thickness T_1 selected to provide the required strength under anticipated loads. The inflow end portion **508** supports an additional layer of material by virtue of the outer skirt **18**. The reduced thickness of the inflow end portion **508** allows the inflow end portion to be crimped to a smaller diameter than the outflow end portion. This offsets or minimizes the increase in the crimp diameter caused by the addition of the outer skirt **18**.

FIGS. **60-62** show an another embodiment of an implantable prosthetic valve **310** that comprises a leaflet structure **314** and a radially collapsible and expandable frame **312** (similar to the frame **50** shown in FIG. **11**) having a plurality of radially spaced commissure windows **318** that are used to secure the leaflet structure within the frame. The valve **310** also comprises a skirt **316** secured between the inner surface of the frame **312** and the curved lower edges **364** of the leaflet structure **314**. The valve **310** has a lower, inflow end **340** and an upper, outflow end **342**.

As shown in FIG. **60**A, each window **318** comprises an enclosed opening **334** between two axially extending side struts **320**, respectively. Each side strut comprises a generally rectangular, e.g. square, cross-sectional profile, as shown in FIG. **63**. Each rectangular side strut **320** comprises four surfaces: an exterior surface **324** on a radially outward facing side, and interior surface **326** on a radially inward facing side, a medial surface **328** on a side facing the other side strut, and a lateral surface **330** on a side facing away from the other side strut. In other embodiments, side struts can comprise other cross-sectional shapes, such circular or hexagonal.

The leaflet structure comprises a plurality of leaflets **360**, each comprising a pair of side tabs **366** secured to the frame **312**, a curved lower edge **364** secured to the skirt **316**, and an articulation portion **372** between the side tabs and the lower edge. Each side tab **366** is paired with an adjacent side tab of another leaflet **360** to form commissures **376** of the leaflet structure **314**. Each pair of side tabs **366** extends radially outwardly through a corresponding commissure window **318** to a location outside of the frame **312** and is secured to the side struts **320** of the window, such as with sutures, as shown in FIG. **62**. In some embodiments, each side tab **366** comprises an end portion **368** (see FIG. **64**) and the two side tab end portions **368** of each commissure **376** extend circumferentially away from one another and along the exterior surfaces **324** of respective side struts **320** of the window **318**.

In some embodiments, each commissure **376** further comprises at least one non-rigid reinforcing sheet **378** sutured to the side tabs **366** and to the side struts **320**. The sheets **378** can comprise a flexible, tear resistant material, including a variety of natural and/or synthetic biocompatible materials. Exemplary synthetic materials can include polymers such as nylon, silicone, and polyesters, including PET. In one example, the sheets **378** comprise a woven PET fabric.

Each reinforcing sheet **378** can be generally rectangular (when laid flat) and can comprise a middle portion **380** and opposing end portions **386**. In some embodiments, a first end portion **386** of the sheet is secured to a first side strut **320** and a second end portion **386** of the sheet is secured to the second side strut **320**, as shown in FIG. **64**. The sheet **378** separates the side tabs **366** from the side struts **320** such that side tabs do not contact the side struts. For example, each end portion **386** of the sheet can be wrapped completely around a respective side strut **320**, as shown in FIG. **64**.

The side tabs **366** and the reinforcing sheet **378** can be secured to the side struts **320** in multiple stages. For example, FIG. **63** shows an exemplary first suturing stage wherein the sheet is positioned such that the middle portion **380** of the sheet extends circumferentially across outer surfaces of the end portions **368** of the side tabs **366** and each end portion **386** of the sheet extends between a respective side tab **366** and the exterior, medial and interior surfaces **324**, **328**, **326**, respectively, of a respective side strut **320**. The sheet **378** surrounds the side tabs **366** and protects the side tabs from edges of the side struts **320**. A pair of in-and-out sutures **390** can secure each side tab **366** and one end of the sheet **378** to a respective strut **320**. As shown in FIG. **63**, each suture **390** can be oriented generally perpendicularly to the circumference of the frame **312** along the lateral surfaces **330** of the side struts **320** and can pass radially back and forth through the commissure **376** at a plurality of difference longitudinal positions. Each suture **390** can intersect a first layer of the sheet **378**, a side tab end portion **368**, a second layer of the sheet, and a third layer of the sheet, in that order moving radially inward. The sutures **390** secure the sheet **378** to the side tab end portions **368** and tighten the sheet end portions **386** around the side struts **320**, thereby securing the side tabs **366** to the side struts **320** and securing the leaflet structure **314** to the frame **312**.

FIG. **64** shows an exemplary second suturing stage wherein a second pair of sutures **392** are used to tie down loose portions of the reinforcing sheet **378**. For example, the second sutures **392** can intersect the portions of the middle portion **380** and the end portions **386** of the sheet that extend laterally beyond the first sutures **390**. The second sutures **392** can be helical whip stitches that intersect the commissures **376** at a plurality of different longitudinal positions, as shown in FIG. **62**, and secure the loose portions of the sheet **378** tightly against the lateral surfaces **330** of the side struts.

Both the first sutures **390** and the second sutures **392** can be positioned adjacent to the lateral surfaces **330** of the struts **320** and spaced away from the window opening **334**. This placement of the sutures can reduce the stress on the sutures caused by movement of the articulation portions **372** of the leaflets. Instead, much of this stress is transferred from flex hinges **370** of the leaflets to the side struts **320** near interior-medial edges **332** of the struts.

The reinforcing sheet **378** protects the flex hinges **370** from damage caused by the interior-medial edges **332** of the struts **320** as the leaflets articulate between open and closed positions, as shown in FIG. **64**. In addition, some embodiments can also include longitudinally extending cushion strips **374** positioned between the flex hinges **370** and the struts **320**, such as adjacent to the interior-medial edges **332**, as shown in FIG. **64**, to further protect the flex hinges from damage caused by the struts. The cushion strips **374** can comprise a flexible, compressible material, such as PET fabric, pericardial tissue, or various other biocompatible materials. In some embodiments, the cushion strips can comprise a tube filled with a resilient material. For example, the cushion strip can comprise a PET tube filled with pericardial tissue. In other embodiments, the outer tubular covering of the cushion strips can be formed from sheet **378** and can be filled with a resilient material. The sheet can be secured around the resilient material with sutures to retain the cushioning strips properly located as shown in FIG. **64**. In other embodiments, separate

cushion strips **374** can be sutured to the reinforcing sheet **378**. The cushion strips **374** can have a thickness similar to the bars **62** to provide a radial clearance between the side struts **320** and the articulating portions **372** of the leaflets to prevent or minimize contact between the leaflets and the inner surface of the frame during the cardiac cycle.

FIG. **65** shows an embodiment similar to FIGS. **63** and **64** but with a different suturing pattern. In FIG. **65**, the sutures **390** are replaced with sutures **398** that secure the sheet **378** around the end portions **368** of the side tabs. Each suture **398** intersects the middle portion **380** of the sheet, one of the side tabs **366**, and a second layer of the sheet adjacent to the medial-exterior edge **324** of each side strut. The sutures **398** can comprise in-and-out stitches that intersect the commissures at a plurality of different longitudinal positions. Each end portion of the sheet **378** can comprise a folded portion **388** that is folded under to form a double layer of the sheet **378** along the surface of the respective side strut **320**. The sutures **392** secure the end portions **386** of the sheet and the end portions **368** of the side tabs tightly around the lateral surfaces **330** of the side struts.

FIGS. **66** and **67** show an alternative method for suturing the side tabs **366** and the sheet **378** to the side struts **320**. FIG. **66** shows suture line **394** positioned along the exterior surfaces **324** of the side struts and generally perpendicular to the radius of the frame. The suture **394** intersects both side tabs **366** and both end portions **386** of the sheet **378**. The suture **394** secures each end portion **386** of the sheet tightly around the medial, interior, and lateral surfaces **328**, **326**, **330**, respectively, of the respective side strut **320**, and also secures the middle portion **380** of the sheet loosely around the end portions **368** of the side tabs **366**. In the embodiment shown in FIG. **66**, the suture **394** intersects a first sheet layer A, a second sheet layer B, the two side tabs **366**, a third sheet layer C, and a fourth sheet layer D, in that order.

After the first suture **394** is in place, the end portions **368** of the side tabs are spread apart and positioned adjacent to the exterior surfaces **324** of the side struts **320**, as shown in FIG. **67**. This tightens the loose middle portion **380** of the sheet around the end portions **368** of the side tabs. A pair of sutures **396** can then secure the middle portion **380** of the sheet tightly to the end portions **386** of the sheet to hold the end portions **368** of the side tabs in place, as shown in FIG. **67**. The sutures **396** can be looping whip stitches that intersect the commissure **376** at a plurality of different longitudinal positions, similar to the sutures **392** in FIG. **64**.

FIGS. **68** and **69** show another alternative method for suturing the side tabs **366** and the sheet **378** to the side struts **320**. FIG. **68** shows a suture line **395** positioned along the exterior side of the window opening and oriented generally perpendicular to the radius of the frame. The suture **395** intersects both side tabs **366** and two portions of the sheet **378**. The suture **395** secures the middle portion **380** of the sheet which extends loosely around the end portions **368** of the side tabs **366**. In the embodiment shown in FIG. **68**, the suture **395** intersects a first sheet layer A, a first side tab B, a second side tab C, and a second sheet layer D, in that order.

After the first suture **395** is in place, the end portions **368** of the side tabs are spread apart and positioned adjacent to the exterior surfaces **324** of the side struts **320**, as shown in FIG. **69**. This tightens the loose middle portion **380** of the sheet around the end portions **368** of the side tabs. A pair of sutures **397** can then secure the middle portion **380** of the sheet tightly to the end portions **386** of the sheet to hold the end portions **368** of the side tabs in place, as shown in FIG. **69**. The end portions **386** of the sheet can comprise a folded under portion **388**, creating a double layer of sheet material to reinforce the sutures **397**. The sutures **397** can be looping whip stitches that intersect the commissure **376** at a plurality of different longitudinal positions, similar to the sutures **392** in FIG. **62**.

FIGS. **70** and **71** show yet another alternative method for suturing the side tabs **366** and the sheet **378** to the side struts **320**. FIG. **70** shows the suture line **395** positioned along the exterior side of the window opening and oriented generally perpendicular to the radius of the frame. The suture **395** intersects both side tabs **366** and four portions or layers of the sheet **378**. Each end portion **386** of the sheet comprises a folded portion **388** that forms a double layer of sheet material between the side tabs **366** and the medial surfaces **328** of the side struts. The suture **395** secures the middle portion **380** of the sheet loosely around the end portions **368** of the side tabs **366**. As shown in FIG. **70**, each stitch of the suture **395** intersects a first pair of sheet layers comprising layers A and B, a first side tab C, a second side tab D, and a second pair of sheet layers comprising layers E and F, in that order.

After the first suture **395** is in place, the end portions **368** of the side tabs are spread apart and positioned adjacent to the exterior surfaces **324** of the side struts **320**, as shown in FIG. **71**. This tightens the middle portion **380** of the sheet around the end portions **368** of the side tabs. A pair of sutures **397** can then secure the middle portion **380** of the sheet tightly to the end portions **386** of the sheet to hold the end portions **368** of the side tabs in place, as shown in FIG. **71**. The folded portions **388** of the sheet create a double layer of sheet material to reinforce the sutures **397**. The sutures **397** can be looping whip stitches that intersect the commissure **376** at a plurality of different longitudinal positions, similar to the sutures **392** in FIG. **62**.

The commissure various configurations for attaching the leaflet structure **314** to the window frames **318** shown in FIGS. **61-71** can also be used as alternative ways to attach the leaflet structure **14** of the valve **10** of FIGS. **1-3** to the window frame portions **30** of frame **12**.

FIGS. **72-74** show a prosthetic heart valve assembly **600** comprising an embodiment of a frame **602** for a prosthetic valve mounted on a balloon **606** of a delivery shaft **604**. The frame **602** can be similar in shape to the frame **12** and can comprise in inflow end portion **610**, an outflow end portion **612** and an intermediate portion **614**. For clarity, the other components of the valve, such as the leaflets and the skirts, are not shown. The frame **602** can have a reduced thickness at the inflow end portion **610** and at the outflow end portion **612**, relative to the thickness of the intermediate portion **614**. Due to the thinner end portions, when the balloon **606** is inflated the end portions **610**, **612** offer less resistance to expansion and expand faster than the intermediate portion **614**, as shown in FIG. **73**. Because the end portions expand faster than the intermediate portion, the frame **602** becomes confined on the balloon **606**, inhibiting the frame from sliding towards either end of the balloon and reducing the risk of the frame sliding off the balloon prematurely. As shown in FIG. **74**, further inflation of the balloon can cause the intermediate portion **614** of the frame to expand to the same final diameter as the end portions **610**, **612** for implantation, after which the balloon can be deflated and removed. Controlling the position of the valve on the balloon can be important during delivery, especially with frames that foreshorten during expansion and move relative to the balloon. In the embodiment shown in FIGS. **72-74**, the intermediate portion **614** of the frame can be held constant relative to the balloon while the two end portions foreshorten towards the intermediate portion due to the "dog-bone" effect of the balloon. Any conventional means can be used to produce the frame **602** with reduced thickness at the end portions **610**, **612**, such as sanding down the end

portions with sand paper or the like. In one embodiment, the end portions **610**, **614** of the frame have a thickness of about 0.37 mm while the intermediate portion **614** has a thickness of about 0.45 mm.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope of these claims.

We claim:

1. An assembly for implanting a prosthetic heart valve in a patient's body comprising:

a delivery apparatus comprising an elongated shaft; and

a radially expandable prosthetic heart valve adapted to be mounted on the shaft in a radially collapsed configuration for delivery into the body, the prosthetic heart valve comprising an annular frame having an inflow end portion defining an inflow end of the frame that is configured to receive antegrade blood flow into the prosthetic heart valve when implanted, and the annular frame also having an outflow end portion defining an outflow end of the frame opposite the inflow end of the frame, the prosthetic heart valve also comprising a leaflet structure positioned within the frame, an inner fabric skirt positioned along an inner surface of the frame, and an outer fabric skirt extending from the inflow end of the frame along an outer surface of the frame to a frame attachment location;

wherein the frame is adapted to shorten axially during radial expansion of the prosthetic valve, thereby increasing axial slack in the outer fabric skirt; and

wherein the outer fabric skirt comprises an edge defining a plurality of alternating projections and notches that is attached to the frame at the frame attachment location.

2. The assembly of claim **1**, wherein an outer diameter of the inflow end portion of the frame is smaller than an outer diameter of the outflow end portion of the frame.

3. The assembly of claim **1**, wherein the leaflet structure comprises a plurality of leaflets, wherein each of the leaflets comprises:

opposing side tabs on opposite sides of the leaflet, the side tabs being secured to the outflow end portion of the frame;

a free outflow edge portion extending between the side tabs adjacent to the outflow end of the frame; and

an inflow edge portion extending between the side tabs adjacent to the inflow end of the frame, the inflow edge portion comprising opposing axial edge portions that extend from the side tabs toward the inflow end of the frame in a generally axial direction and an intermediate edge portion that extends between the axial edge portions, the intermediate edge portion comprising a curved apex portion adjacent to the inflow end of the frame and a pair of oblique portions that extend between the axial edge portions and the apex portion, the oblique portions having a greater radius of curvature than the apex portion.

4. The assembly of claim **1**, wherein the frame comprises three angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts; and

the leaflet structure comprises a plurality of leaflets each comprising two opposing side tabs, each side tab being paired with an adjacent side tab of an adjacent leaflet to form commissures of the leaflet structure, and wherein each commissure extends radially outwardly through a corresponding commissure window of the frame to a location outside of the frame and is sutured to the side struts of the commissure window.

5. The assembly of claim **4**, wherein the commissure windows of the frame are depressed radially inwardly relative to the portions of the frame extending between adjacent commissure windows when the prosthetic valve is in the radially collapsed configuration on the shaft.

6. The assembly of claim **1**, wherein the frame comprises an inflow row of openings at the inflow end portion of the frame, an outflow row of openings at the outflow end portion of the frame, and at least one intermediate row of openings between the inflow row of openings and the outflow row of openings;

wherein the openings of the inflow row of openings are larger than the openings of the at least one intermediate row of openings.

7. The assembly of claim **1**, wherein the frame has a plurality of openings and portions of the leaflet structure protrude through the openings while the prosthetic valve is in the radially collapsed configuration.

8. The assembly of claim **1**, wherein the inflow end portion of the frame comprises a frame thickness that is less than a frame thickness of an intermediate portion of the frame between the inflow end portion and the outflow end portion.

9. The valve of claim **1**, wherein the outer fabric skirt extends from the inflow end of the frame along the outer surface of the frame to a plurality of outer skirt attachment locations on the outer surface of frame, and wherein distances from the inflow end of the frame to the plurality of outer skirt attachment locations become smaller when the prosthetic heart valve is radially expanded.

10. The valve of claim **9**, wherein when the prosthetic heart valve is radially expanded, the plurality of outer skirt attachment locations and the inflow end of the frame are at substantially the same radial distance from a longitudinal center axis of the prosthetic heart valve.

11. The valve of claim **1**, wherein the projections at the edge of the outer skirt are attached to the frame and the notches in the edge of the outer skirt are not attached to the frame.

12. An assembly for implanting a prosthetic heart valve in a patient's body comprising:

a delivery apparatus comprising an elongated shaft;

a radially expandable and collapsible prosthetic heart valve mounted on the shaft in a radially collapsed configuration for delivery into the body, the prosthetic heart valve comprising an annular frame and a leaflet structure within the frame;

wherein the frame comprises a plurality of angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts, and the frame further comprises intermediate side struts that are axially oriented and positioned angularly between the commissure windows, and the leaflet structure comprises a plurality of commissure portions that extend outwardly through respective commissure windows to locations outside of the frame; and

wherein the commissure windows are depressed radially inwardly relative to the intermediate side struts when the prosthetic heart valve is radially collapsed on the shaft, such that an outermost surface of each commissure portion of the leaflet structure outside of the frame is at substantially the same radial distance from a longitudi-

nal center axis of the prosthetic heart valve as outer surfaces of the intermediate side struts.

13. The valve of claim **12**, wherein the commissure windows of the frame are depressed inwardly a radial distance of between 0.2 mm and 1.0 mm relative to the intermediate side struts when the valve is radially collapsed.

14. The valve of claim **12**, wherein an outer diameter of an inflow end portion of the frame is smaller than an outer diameter of an outflow end portion of the frame when the valve is radially collapsed on the shaft.

15. The assembly of claim **12**, wherein an outer surface of the frame defines radial depressions in regions proximate the commissure windows, and outer portions of the commissure portions of the leaflet structure are located in the radial depressions along the outside of the frame.

16. The assembly of claim **12**, wherein the commissure portions of the leaflet structure are sutured to the axially oriented side struts of the commissure windows.

17. An implantable prosthetic valve that is radially collapsible to a collapsed configuration and radially expandable to an expanded configuration, the prosthetic valve comprising:

an annular frame having a longitudinal axis extending between an inflow end of the frame and an outflow end of the frame and defining an axial direction, the inflow end of the frame being configured to receive antegrade blood flow into the prosthetic valve when implanted;

a leaflet structure positioned within the frame; and

an annular outer skirt positioned around an outer surface of the frame, the outer skirt comprising an inflow edge positioned at a first location at the inflow end of the frame, an outflow edge defining a plurality of spaced apart axial projections that are secured to the frame at a second location axially spaced from the inflow edge, and an intermediate portion extending between the inflow edge and the outflow edge and positioned outside of the frame;

wherein when the valve is in the expanded configuration, the intermediate portion of the outer skirt comprises slack in the axial direction between the inflow edge of the outer skirt and the outflow edge of the outer skirt, and when the valve is collapsed to the collapsed configuration, the distance between the inflow edge of the outer skirt and the outflow edge of the outer skirt increases, reducing the slack in the outer skirt in the axial direction.

18. The valve of claim **17**, wherein the outflow edge of the outer skirt comprises a plurality of alternating projections and notches, the projections being secured to the frame at the second location, the outer skirt being unsecured to the frame at the notches.

19. The valve of claim **17**, wherein the outer skirt is not stretched in the axial direction when the valve is radially collapsed to the collapsed configuration and slack is removed from the intermediate portion of the outer skirt.

20. An implantable prosthetic valve comprising:

an annular frame comprising a plurality of leaflet attachment portions; and

a leaflet structure positioned within the frame and secured to the leaflet attachment portions of the frame, the leaflet structure comprising a plurality of leaflets, each leaflet comprising a body portion having a free outflow edge, two opposing primary side tabs extending from opposite sides of the body portion, and two opposing secondary tabs, each secondary tab extending from the body portion adjacent to a respective primary side tab, the secondary tabs extending from the body portion at opposite ends of the free outflow edge;

wherein the secondary tabs are folded about radially extending creases that extend radially from the opposite ends of the free outflow edge, such that a first portion of the secondary tabs lies flat against the body portion of the respective leaflet, and the secondary tabs are folded about axially extending creases such that a second portion of the secondary tabs extends in a different plane than the first portion, wherein the radially extending creases and the axially extending creases are non-parallel.

21. The valve of claim **20**, wherein the second portion of each secondary tab is sutured to a respective primary tab.

22. The valve of claim **20**, wherein the secondary tabs are positioned inside of the frame.

23. The valve of claim **20**, wherein the first portion of each the secondary tab pivots about the axially extending crease and lays flat against the second portion of the secondary tab when the valve is collapsed to a radially collapsed configuration.

24. The valve of claim **20**, wherein the first portion of each secondary tab extends radially inwardly from the frame and comprises an inner edge spaced radially from an inner surface of the frame, and the body portion of the leaflet articulates about the inner edges of the two secondary tabs of the leaflet in response to blood flowing through the valve when the valve is in operation within a patient's body.

25. The valve of claim **20**, wherein the plurality of leaflet attachment portions comprises window frame portions each comprising an enclosed opening between first and second axially oriented side struts, and wherein the primary side tabs extend radially outwardly through respective window frame portions to a location outside of the frame and are sutured to the secondary tabs to secure the leaflets around the side struts.

* * * * *

US009119716B2

(12) **United States Patent**
Lee et al.

(10) **Patent No.: US 9,119,716 B2**
(45) **Date of Patent: Sep. 1, 2015**

(54) **DELIVERY SYSTEMS FOR PROSTHETIC HEART VALVE**

(75) Inventors: **Walter Lee**, Irvine, CA (US); **Mark Dehdashtian**, Irvine, CA (US); **Teodoro S. Jimenez**, Irvine, CA (US); **Gilbert S. Leung**, La Verne, CA (US); **Bryan Janish**, Irvine, CA (US); **Michael G. Valdez**, Riverside, CA (US); **Tram Nguyen**, Santa Ana, CA (US); **Timothy C. Ulrich**, Rancho Santa Margarita, CA (US)

(73) Assignee: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 83 days.

(21) Appl. No.: **13/559,395**

(22) Filed: **Jul. 26, 2012**

(65) **Prior Publication Data**

US 2013/0030520 A1 Jan. 31, 2013

Related U.S. Application Data

(60) Provisional application No. 61/512,328, filed on Jul. 27, 2011.

(51) **Int. Cl.**
A61F 2/24 (2006.01)
A61F 2/06 (2013.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61F 2/2433*** (2013.01); *A61F 2002/9517* (2013.01); *A61F 2002/9586* (2013.01); *A61M 25/1002* (2013.01); *A61M 2025/1013* (2013.01); *A61M 2025/1084* (2013.01)

(58) **Field of Classification Search**
CPC A61F 2/958; A61F 2002/9583; A61F 2002/9586; A61F 2002/9522
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,409,013 A 11/1968 Berry
3,472,230 A 10/1969 Fogarty et al.
(Continued)

FOREIGN PATENT DOCUMENTS

DE 2246526 3/1973
DE 19532846 3/1997
(Continued)

OTHER PUBLICATIONS

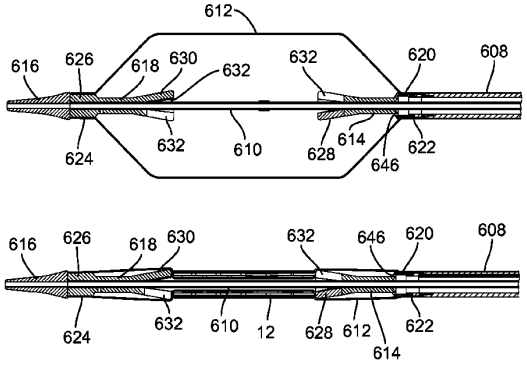
Andersen, et al., "Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs." European Heart Journal (1992), 13, 704-708.
(Continued)

Primary Examiner — Elizabeth Houston
Assistant Examiner — Michael Mendoza
(74) *Attorney, Agent, or Firm* — AnneMarie Kaiser; David L. Hauser

(57) **ABSTRACT**

Described herein are systems and methods from delivering prosthetic devices, such as prosthetic heart valves, through the body and into the heart for implantation therein. The prosthetic devices delivered with the delivery systems disclosed herein are, for example, radially expandable from a radially compressed state mounted on the delivery system to a radially expanded state for implantation using an inflatable balloon of the delivery system. Exemplary delivery routes through the body and into the heart include transfemoral routes, transapical routes, and transaortic routes, among others.

12 Claims, 19 Drawing Sheets



(51) **Int. Cl.**

A61F 2/95	(2013.01)
A61F 2/958	(2013.01)
A61M 25/10	(2013.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,548,417	A		12/1970	Kisher
3,587,115	A		6/1971	Shiley
3,657,744	A		4/1972	Ersek
3,671,979	A		6/1972	Moulopoulos
3,714,671	A		2/1973	Edwards et al.
3,755,823	A		9/1973	Hancock
4,035,849	A		7/1977	Angell et al.
4,056,854	A		11/1977	Boretos et al.
4,106,129	A		8/1978	Carpentier et al.
4,222,126	A		9/1980	Boretos et al.
4,265,694	A		5/1981	Boretos et al.
4,297,749	A		11/1981	Davis et al.
4,339,831	A		7/1982	Johnson
4,343,048	A		8/1982	Ross et al.
4,345,340	A		8/1982	Rosen
4,373,216	A		2/1983	Klawitter
4,406,022	A		9/1983	Roy
4,470,157	A		9/1984	Love
4,535,483	A		8/1985	Klawitter et al.
4,574,803	A		3/1986	Storz
4,592,340	A		6/1986	Boyles
4,605,407	A		8/1986	Black et al.
4,612,011	A		9/1986	Kautzky
4,643,732	A		2/1987	Pietsch et al.
4,655,771	A		4/1987	Wallsten
4,692,164	A		9/1987	Dzemeshkevich et al.
4,733,665	A		3/1988	Palmaz
4,759,758	A		7/1988	Gabbay
4,762,128	A		8/1988	Rosenbluth
4,777,951	A		10/1988	Cribier et al.
4,787,899	A		11/1988	Lazarus
4,787,901	A		11/1988	Baykut
4,796,629	A		1/1989	Grayzel
4,829,990	A		5/1989	Thuroff et al.
4,851,001	A		7/1989	Taheri
4,856,516	A		8/1989	Hillstead
4,878,495	A		11/1989	Grayzel
4,878,906	A		11/1989	Lindemann et al.
4,883,458	A		11/1989	Shiber
4,922,905	A		5/1990	Strecker
4,955,895	A		9/1990	Sugiyama et al.
4,966,604	A		10/1990	Reiss
4,979,939	A		12/1990	Shiber
4,986,830	A		1/1991	Owens et al.
4,994,077	A		2/1991	Dobben
5,007,896	A		4/1991	Shiber
5,026,366	A		6/1991	Leckrone
5,032,128	A		7/1991	Alonso
5,037,434	A		8/1991	Lane
5,047,041	A		9/1991	Sammuels
5,059,177	A		10/1991	Towne et al.
5,080,668	A		1/1992	Bolz et al.
5,085,635	A		2/1992	Cragg
5,089,015	A		2/1992	Ross
5,152,771	A		10/1992	Sabbaghian et al.
5,163,953	A		11/1992	Vince
5,167,628	A		12/1992	Boyles
5,176,698	A		1/1993	Burns et al.
5,192,297	A		3/1993	Hull
5,266,073	A		11/1993	Wall
5,282,847	A		2/1994	Trescony et al.
5,295,958	A		3/1994	Shturman
5,332,402	A		7/1994	Teitelbaum
5,358,496	A		10/1994	Ortiz et al.
5,360,444	A		11/1994	Kusuhara
5,370,685	A		12/1994	Stevens
5,397,351	A		3/1995	Pavcnik et al.
5,411,055	A		5/1995	Kane et al.
5,411,552	A		5/1995	Andersen et al.
5,443,446	A		8/1995	Shturman
5,480,424	A		1/1996	Cox
5,500,014	A		3/1996	Quijano et al.
5,545,209	A		8/1996	Roberts et al.
5,545,214	A		8/1996	Stevens
5,549,665	A		8/1996	Vesely
5,554,185	A		9/1996	Block et al.
5,571,175	A		11/1996	Vanney et al.
5,591,185	A		1/1997	Kilmer et al.
5,599,305	A		2/1997	Hermann et al.
5,607,464	A		3/1997	Trescony et al.
5,609,626	A		3/1997	Quijano et al.
5,632,760	A	*	5/1997	Sheiban et al. 606/191
5,639,274	A		6/1997	Fischell et al.
5,665,115	A		9/1997	Cragg
5,716,417	A		2/1998	Girard et al.
5,728,068	A		3/1998	Leone et al.
5,749,890	A		5/1998	Shaknovich
5,756,476	A		5/1998	Epstein
5,769,812	A		6/1998	Stevens et al.
5,800,508	A		9/1998	Goicoechea et al.
5,840,081	A		11/1998	Andersen et al.
5,855,597	A		1/1999	Jayaraman
5,855,601	A		1/1999	Bessler
5,855,602	A		1/1999	Angell
5,908,405	A		6/1999	Imran et al.
5,925,063	A		7/1999	Khosravi
5,957,949	A		9/1999	Leonhardt et al.
5,968,068	A		10/1999	Dehdashtian
5,968,069	A	*	10/1999	Dusbabek et al. 606/194
6,027,510	A	*	2/2000	Alt 606/108
6,027,525	A		2/2000	Suh et al.
6,033,381	A		3/2000	Kontos
6,042,607	A		3/2000	Williamson, IV et al.
6,132,473	A		10/2000	Williams et al.
6,168,614	B1		1/2001	Andersen et al.
6,171,335	B1		1/2001	Wheatley et al.
6,174,327	B1		1/2001	Mertens et al.
6,210,408	B1		4/2001	Chandrasakaran et al.
6,217,585	B1		4/2001	Houser et al.
6,221,091	B1		4/2001	Khosravi
6,231,602	B1		5/2001	Carpentier et al.
6,235,050	B1		5/2001	Quiachon et al.
6,245,102	B1		6/2001	Jayaraman
6,264,683	B1		7/2001	Stack et al.
6,299,637	B1		10/2001	Shaolian
6,302,906	B1		10/2001	Goicoechea et al.
6,350,277	B1		2/2002	Kocur
6,379,372	B1		4/2002	Dehdashtian et al.
6,425,916	B1		7/2002	Garrison et al.
6,440,164	B1		8/2002	Di Matteo et al.
6,454,799	B1		9/2002	Schreck
6,458,153	B1		10/2002	Bailey et al.
6,461,382	B1		10/2002	Cao
6,468,660	B2		10/2002	Ogle
6,482,228	B1		11/2002	Norred
6,488,704	B1		12/2002	Connelly et al.
6,514,228	B1		2/2003	Hamilton et al.
6,569,196	B1		5/2003	Vesely et al.
6,579,305	B1		6/2003	Lashinski
6,582,462	B1		6/2003	Andersen et al.
6,605,112	B1		8/2003	Moll
6,730,118	B2		5/2004	Spenser et al.
6,733,525	B2		5/2004	Yang et al.
6,764,504	B2	*	7/2004	Wang et al. 623/1.11
6,830,584	B1		12/2004	Seguin
6,893,460	B2		5/2005	Spenser et al.
6,908,481	B2		6/2005	Cribier
7,018,406	B2		3/2006	Seguin et al.
7,276,078	B2		10/2007	Spenser et al.
7,276,084	B2		10/2007	Yang et al.
7,318,278	B2		1/2008	Zhang et al.
7,374,571	B2		5/2008	Pease et al.
7,381,210	B2		6/2008	Zarbatany et al.
7,393,360	B2		7/2008	Spenser et al.
7,462,191	B2		12/2008	Spenser et al.
7,510,575	B2		3/2009	Spenser et al.
7,579,381	B2		8/2009	Dove
7,585,321	B2		9/2009	Cribier

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,594,926	B2	9/2009	Linder et al.
7,597,709	B2	10/2009	Goodin
7,618,446	B2	11/2009	Andersen et al.
7,621,948	B2	11/2009	Herrmann
7,993,394	B2	8/2011	Hariton et al.
8,007,992	B2	8/2011	Tian et al.
8,029,556	B2	10/2011	Rowe
8,167,932	B2	5/2012	Bourang
RE43,882	E	12/2012	Hopkins et al.
8,407,380	B2	3/2013	Matsunaga
8,568,472	B2	10/2013	Marchand et al.
2001/0021872	A1	9/2001	Bailey et al.
2002/0032481	A1	3/2002	Gabbay
2002/0173842	A1	11/2002	Buchanan
2003/0050694	A1	3/2003	Yang et al.
2003/0100939	A1	5/2003	Yodfat et al.
2003/0158597	A1	8/2003	Quiachon
2003/0212454	A1	11/2003	Scott et al.
2004/0039436	A1	2/2004	Spenser et al.
2004/0098081	A1	5/2004	Landreville et al.
2004/0102791	A1	5/2004	Murray
2004/0133263	A1	7/2004	Dusbabek et al.
2004/0186563	A1	9/2004	Lobbi
2004/0186565	A1	9/2004	Schreck
2004/0260389	A1	12/2004	Case et al.
2005/0203614	A1	9/2005	Forster et al.
2005/0203617	A1	9/2005	Forster et al.
2005/0234546	A1	10/2005	Nugent et al.
2005/0245894	A1	11/2005	Zadno-Azizi
2005/0288766	A1	12/2005	Plain et al.
2006/0025857	A1	2/2006	Bergheim et al.
2006/0149350	A1	7/2006	Patel et al.
2006/0229719	A1	10/2006	Marquez et al.
2006/0259137	A1	11/2006	Artof et al.
2006/0282150	A1	12/2006	Olson et al.
2007/0005131	A1	1/2007	Taylor
2007/0005231	A1	1/2007	Seguchi
2007/0010877	A1	1/2007	Salahieh et al.
2007/0027534	A1	2/2007	Bergheim et al.
2007/0088431	A1	4/2007	Bourang et al.
2007/0112422	A1	5/2007	Dehdashtian
2007/0203575	A1	8/2007	Forster et al.
2007/0270943	A1	11/2007	Solem
2008/0065011	A1	3/2008	Marchand et al.
2008/0114442	A1	5/2008	Mitchell et al.
2008/0119922	A1	5/2008	Alkhatib
2008/0125853	A1	5/2008	Bailey et al.
2008/0154355	A1	6/2008	Benichou et al.
2008/0161911	A1	7/2008	Revuelta et al.
2009/0124428	A1	5/2009	Sullivan et al.
2009/0138079	A1	5/2009	Tuval et al.
2009/0157175	A1	6/2009	Benichou
2009/0164005	A1	6/2009	Dove et al.
2009/0171456	A1	7/2009	Kveen et al.
2009/0192585	A1	7/2009	Bloom et al.
2009/0234428	A1	9/2009	Snow et al.
2009/0281619	A1	11/2009	Le et al.
2009/0299456	A1	12/2009	Melsheimer
2009/0319037	A1	12/2009	Rowe et al.
2010/0030318	A1	2/2010	Berra
2010/0036472	A1	2/2010	Papp
2010/0036473	A1	2/2010	Roth
2010/0049313	A1	2/2010	Alon et al.
2010/0076402	A1	3/2010	Mazzone et al.
2010/0076541	A1	3/2010	Kumoyama
2010/0082089	A1	4/2010	Quadri et al.
2010/0094394	A1	4/2010	Beach et al.
2010/0121425	A1	5/2010	Shimada
2010/0145431	A1	6/2010	Wu et al.
2010/0174363	A1	7/2010	Castro
2010/0204781	A1	8/2010	Alkhatib
2010/0274344	A1	10/2010	Dusbabek et al.
2011/0015729	A1	1/2011	Jimenez et al.
2011/0054596	A1	3/2011	Taylor
2011/0160846	A1	6/2011	Bishop et al.
2012/0123529	A1	5/2012	Levi et al.
2013/0218266	A1	8/2013	Chalekian et al.

FOREIGN PATENT DOCUMENTS

DE	19546692	6/1997
DE	19857887	7/2000
DE	19907646	8/2000
DE	10049812	4/2002
DE	10049813	4/2002
DE	10049814	4/2002
DE	10049815	4/2002
EP	0103546	3/1984
EP	0144167	6/1985
EP	0597967	12/1994
EP	0592410	10/1995
EP	0850607	7/1998
EP	1057460	12/2000
EP	1088529	4/2001
EP	1570809	9/2005
FR	2788217	7/2007
GB	2056023	3/1981
SU	1271508	11/1986
WO	WO 91/17720	11/1991
WO	WO 92/17118	10/1992
WO	WO 93/01768	2/1993
WO	WO 97/24080	7/1997
WO	WO 98/29057	7/1998
WO	WO 99/33414	7/1999
WO	WO 99/40964	8/1999
WO	WO 99/47075	9/1999
WO	WO 00/18333	4/2000
WO	WO 00/41652	7/2000
WO	WO 00/47139	8/2000
WO	WO 01/35878	5/2001
WO	WO 01/49213	7/2001
WO	WO 01/54624	8/2001
WO	WO 01/54625	8/2001
WO	WO 01/62189	8/2001
WO	WO 01/64137	9/2001
WO	WO 01/76510	10/2001
WO	WO 02/22054	3/2002
WO	WO 02/36048	5/2002
WO	WO 02/41789	5/2002
WO	WO 02/43620	6/2002
WO	WO 02/47575	6/2002
WO	WO 02/49540	6/2002
WO	WO 03/047468	6/2003
WO	WO 2005/087140	9/2005
WO	WO 2005/102015	11/2005
WO	WO 2006/014233	2/2006
WO	WO 2006/034008	3/2006
WO	WO 2006/108090	10/2006
WO	WO 2006/138173	12/2006
WO	WO 2008/005405	1/2008
WO	WO 2008/035337	3/2008
WO	WO 2008/147964	12/2008
WO	WO 2008/150529	12/2008
WO	WO 2009/116041	9/2009

OTHER PUBLICATIONS

Andersen, Henning Rud, "History of Percutaneous Aortic Valve Prosthesis," Herz 34 2009 Nr. 5, Urban & Vogel, pp. 343-346, Skejby University Hospital Department of Cardiology, Aarhus, Denmark.

Almagor, M.D., Yaron, et al., "Balloon Expandable Stent Implantation in Stenotic Right Heart Valved Conduits," Journal of the American College of Cardiology, vol. 16, No. 6, pp. 1310-1314, Nov. 1, 1990; ISSN 0735-1097.

Sabbah, Ph.D., Hani N., et al., "Mechanical Factors in the Degeneration of Porcine Bioprosthetic Valves: An Overview," Journal of Cardiac Surgery, vol. 4, No. 4, pp. 302-309, Dec. 1989; ISSN 0886-0440.

Serruys, P.W., et al., "Stenting of Coronary Arteries. Are we the Sorcerer's Apprentice?," European Heart Journal (1989) 10, 774-782, pp. 37-45, Jun. 13, 1989.

Kolata, Gina, "Device That Opens Clogged Arteries Gets a Failing Grade in a New Study," nytimes.com, http://www.nytimes.

(56) **References Cited**

OTHER PUBLICATIONS

com/1991/01/03/health/device-that-opens-clowed-arteries-gets-a-faili . . . , Jul. 29, 2009, 2 pages.
Urban, M.D., Philip, "Coronary Artery Stenting," Editions Médecine et Hygiène, Genève, 1991, pp. 5-47.
Al-Khaja, N., et al., "Eleven Years' Experience with Carpentier-Edwards Biological Valves in Relation to Survival and Complications," European Journal of Cardiothoracic Surgery 3:305-311, Jun. 30, 2009.
Wheatley, M.D., David J., "Valve Prostheses," Rob & Smith's Operative Surgery, Fourth Edition, pp. 415-424, Butterworths 1986.
Benchimol, Alberto, et al., "Simultaneous Left Ventricular Echocardiography and Aortic Blood Velocity During Rapid Right Ventricular Pacing in Man," The American Journal of the Medical Sciences, Jan.-Feb. 1977 vol. 273, No. 1, pp. 55-62.
Watt, A.H., et al. "Intravenous Adenosine in the Treatment of Supraventricular Tachycardia; a Dose-Ranging Study and Interaction with Dipyridamole," British Journal of Clinical Pharmacology (1986), 21, 227-230.
Uchida, Barry T., et al., "Modifications of Gianturco Expandable Wire Stents," AJR:150, May 1988, Dec. 3, 1987, pp. 1185-1187.
Selby, M.D., J. Bayne, "Experience with New Retrieval Forceps for Foreign Body Removal in the Vascular, Urinary, and Biliary Systems," Radiology 1990; 176:535-538.
Inoune, M.D., Kanji, et al., "Clinical Application of Transvenous Mitral Commissurotomy by a New Balloon Catheter," The Journal of Thoracic and Cardiovascular Surgery 87:394-402, 1984.
Al Zaibag, Muayed, et al., "Percutaneous Balloon Valvotomy in Tricuspid Stenosis," British Heart Journal, Jan. 1987, vol. 57, No. 1, pp. 51-53.
Lawrence, Jr., M.D., David D., "Percutaneous Endovascular Graft: Experimental Evaluation," Radiology 1897; 163: 357-360.
Dotter, M.D., Charles T., "Transluminal Treatment of Arteriosclerotic Obstruction," University of Oregon's Minthorn Memorial Laboratory for Cardiovascular Research through Radiology, Circulation, vol. XXX, Nov. 1964, pp. 654-670.
Sigwart, Ulrich, "An Overview of Intravascular Stents: Old and New," Chapter 48, Textbook of Interventional Cardiology, 2nd Edition, W.B. Saunders Company, Philadelphia, PA, © 1994, 1990, pp. 803-815.
M.D. Dake, New Engl.J.Med. 1994;331:1729-34.
Rashkind, M.D., William J., "Historical Aspects of Interventional Cardiology: Past, Present, Future," Texas Heart Institute Journal, Interventional Cardiology, pp. 363-367.
Rosch, M.D., Josef, "The Birth, Early Years and Future of Interventional Radiology," J Vasc Intent Radiol 2003; 14:841-853.
Pavcnik, M.D., Ph.D., Dusan, et al. "Development and Initial Experimental Evaluation of a Prosthetic Aortic Valve for Transcatheter Placement," Cardiovascular Radiology 1992; 183:151-154.
Ross, F.R.C.S., D.N., "Aortic Valve Surgery," Guy's Hospital, London, pp. 192-197, approximately 1968.
Rashkind, M.D., William J., "Creationof an Atrial Septal Defect Withoput Thoracotomy," the Journal of the American Medical Association, vol. 196, No. 11, Jun. 13, 1966, pp. 173-174.
Porstmann, W., et al., "Der Verschluβ des Ductus Arteriosus Persistens ohne Thorakotomie," Thoraxchirurgie Vaskuläre Chirurgie, Band 15, Heft 2, Stuttgart, im Apr. 1967, pp. 199-203.

* cited by examiner

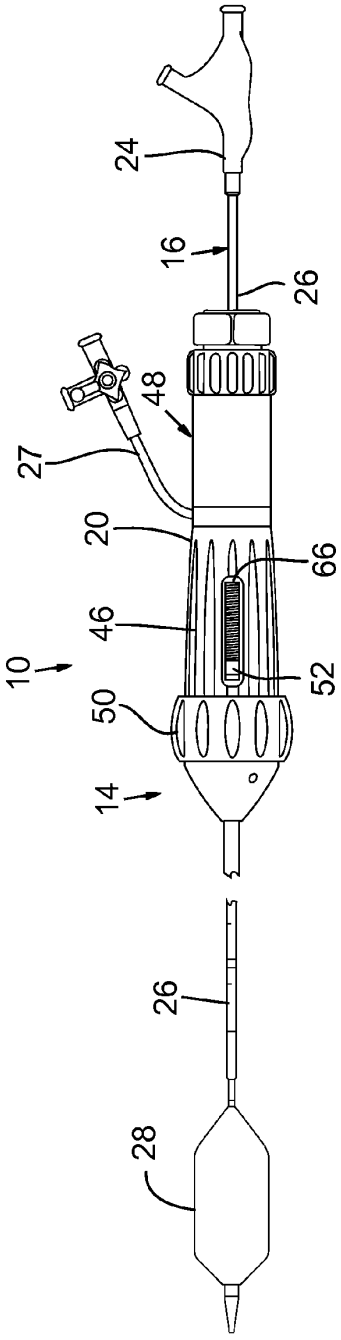

24
16
26
48
27
20
66
46
10
52
50
14
26
28

FIG. 1

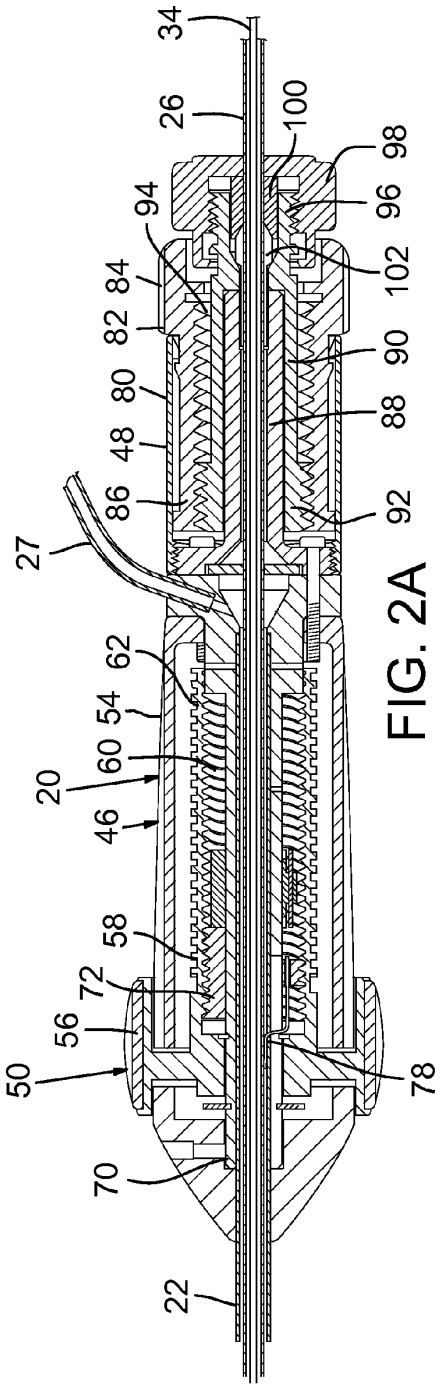

34
26
100
98
94
96
102
84
82
90
80
88
48
86
92
27
62
54
60
20
46
58
72
56
50
78
70
22

FIG. 2A

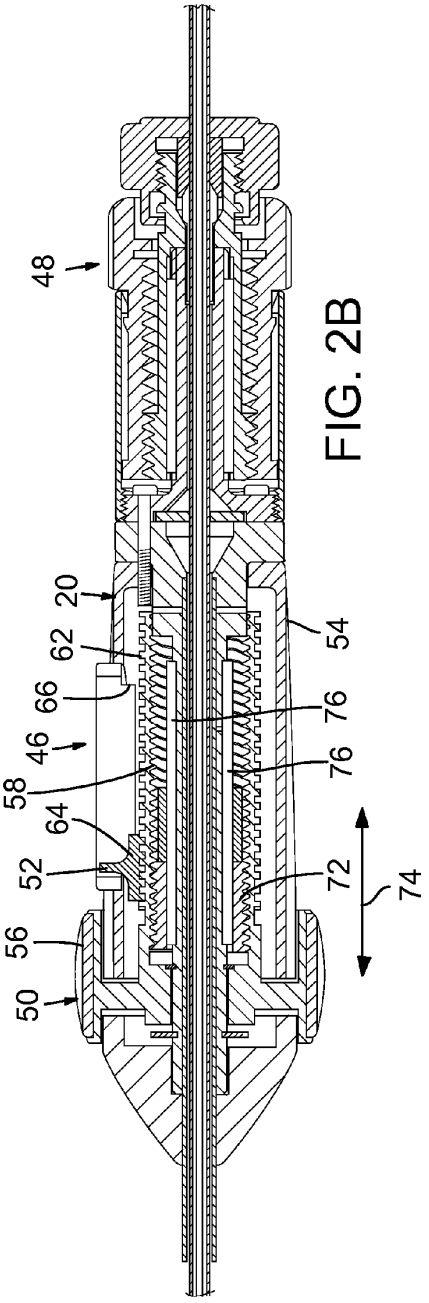


FIG. 2B

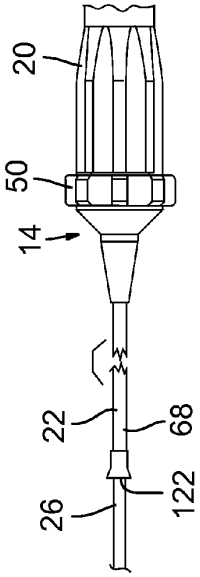


FIG. 3

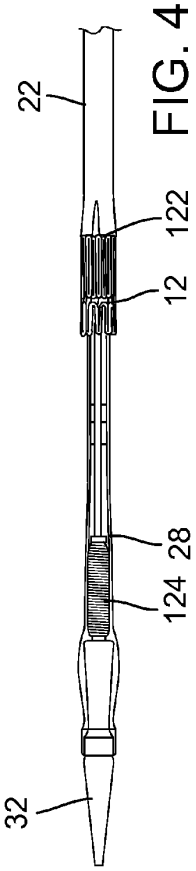


FIG. 4

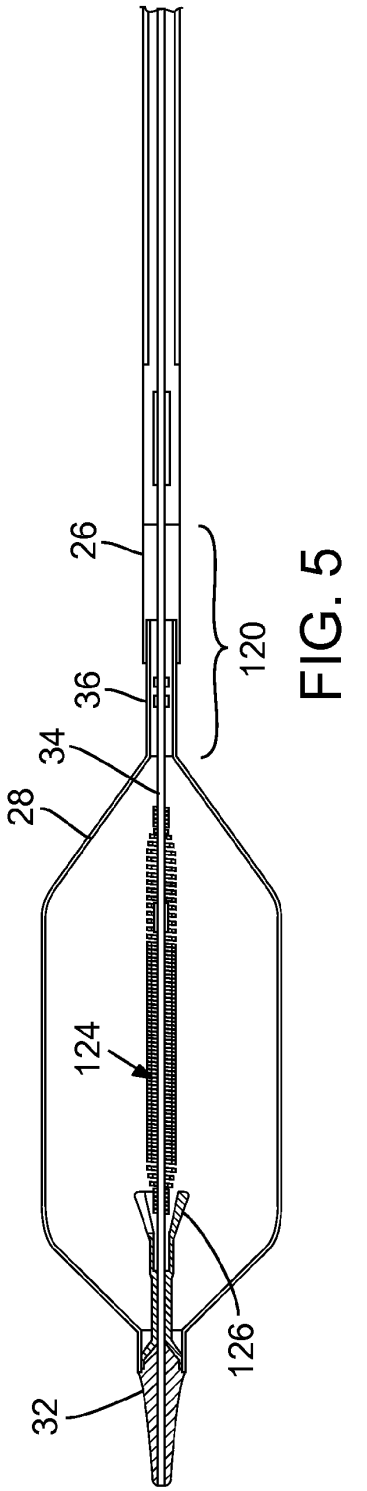


FIG. 5

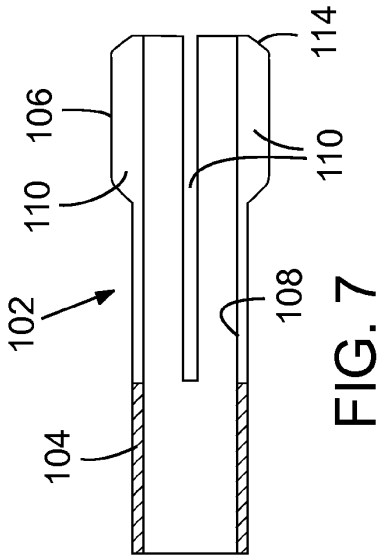


FIG. 7

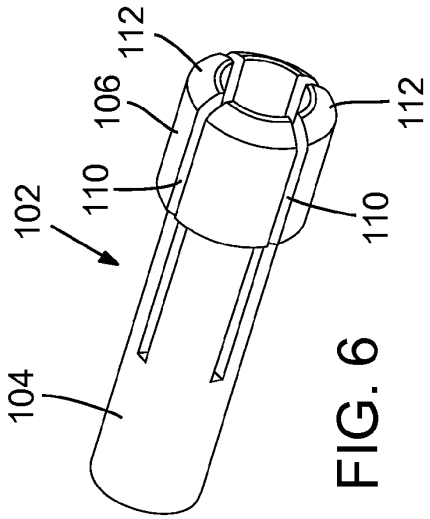


FIG. 6

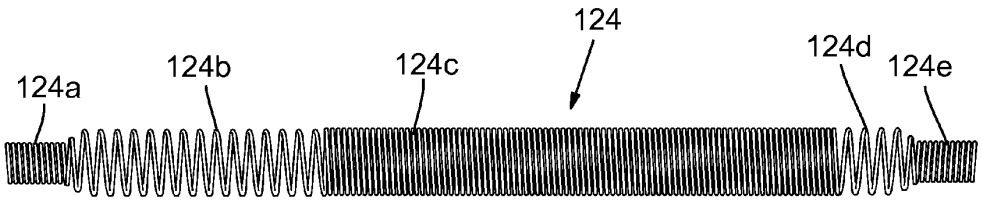


FIG. 8

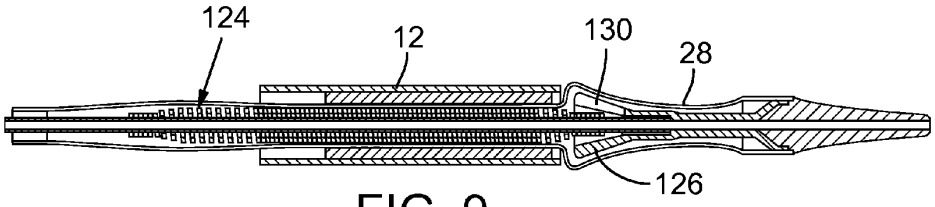


FIG. 9

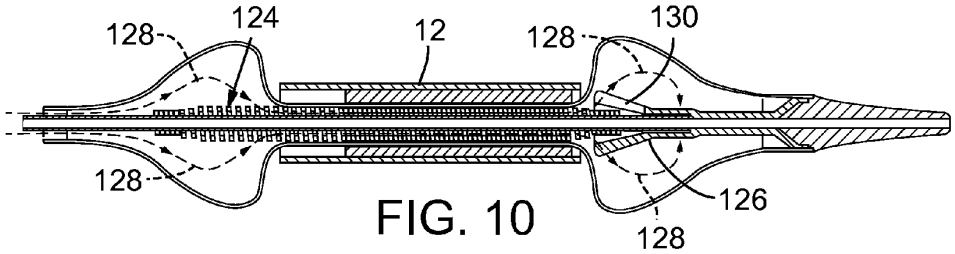


FIG. 10

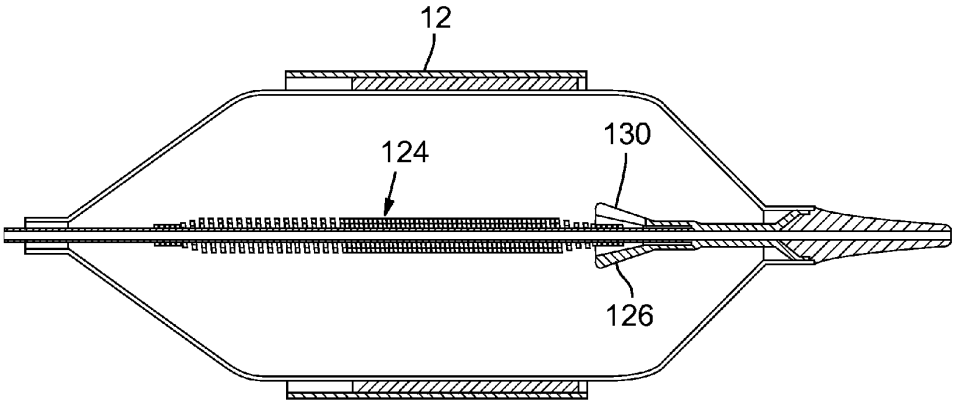


FIG. 11

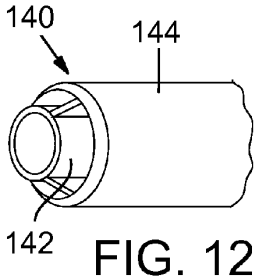


FIG. 12

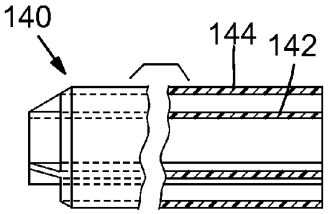


FIG. 13

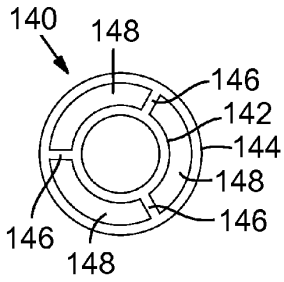


FIG. 14

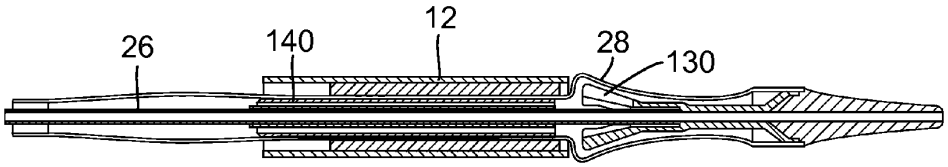


FIG. 15

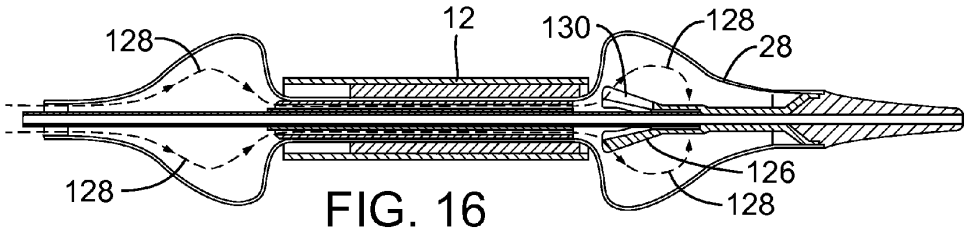


FIG. 16

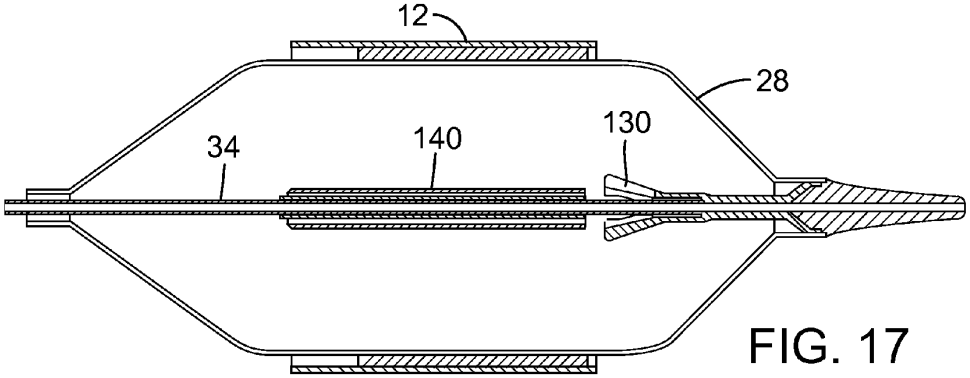


FIG. 17

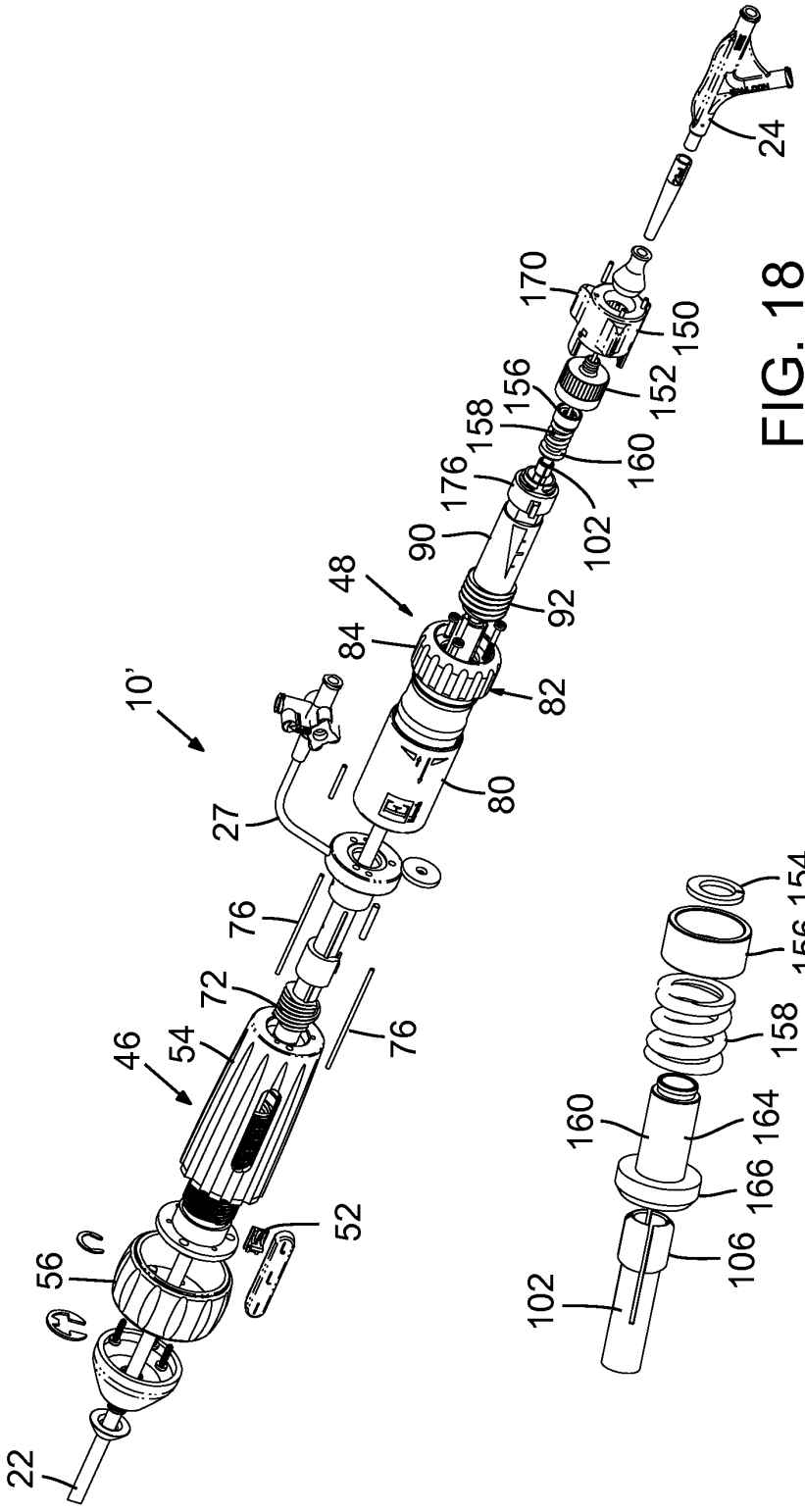

24
170
150
152
156
158
160
176
102
90
92
48
84
82
80
10'
27
76
72
46
54
52
56
22

FIG. 18

154
156
158
160
164
166
106
102

FIG. 19

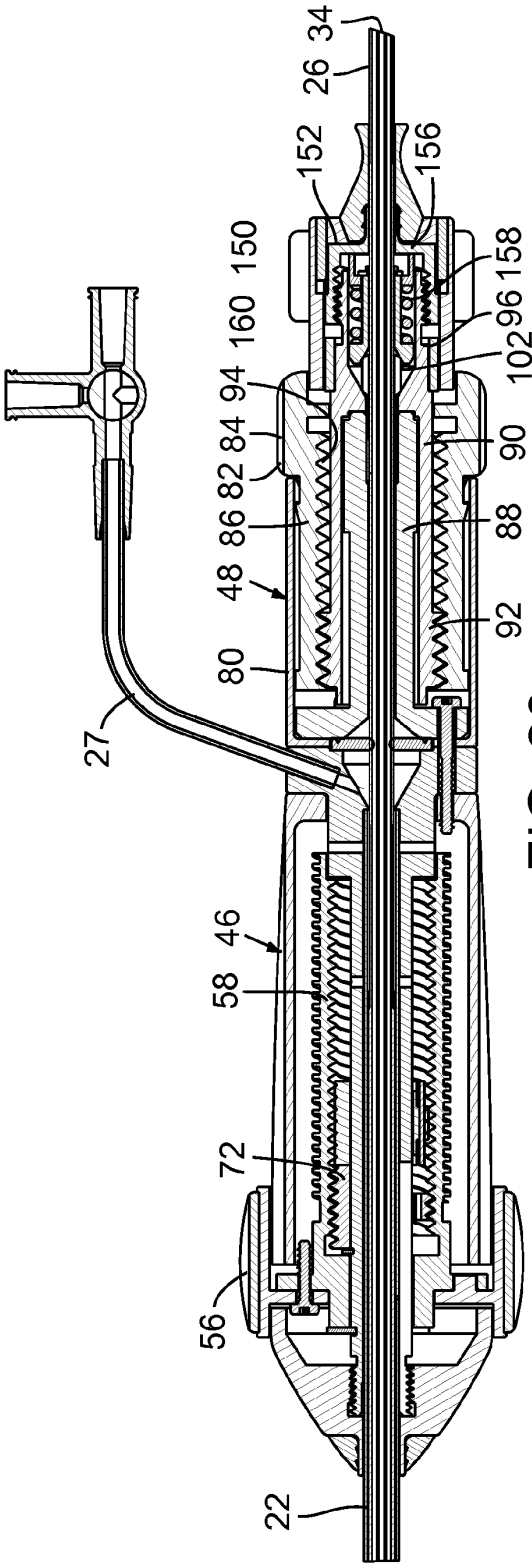

34
26
152
156
150
160
158
96
102
94
84
82
86
48
80
90
88
92
27
46
58
72
56
22

FIG. 20

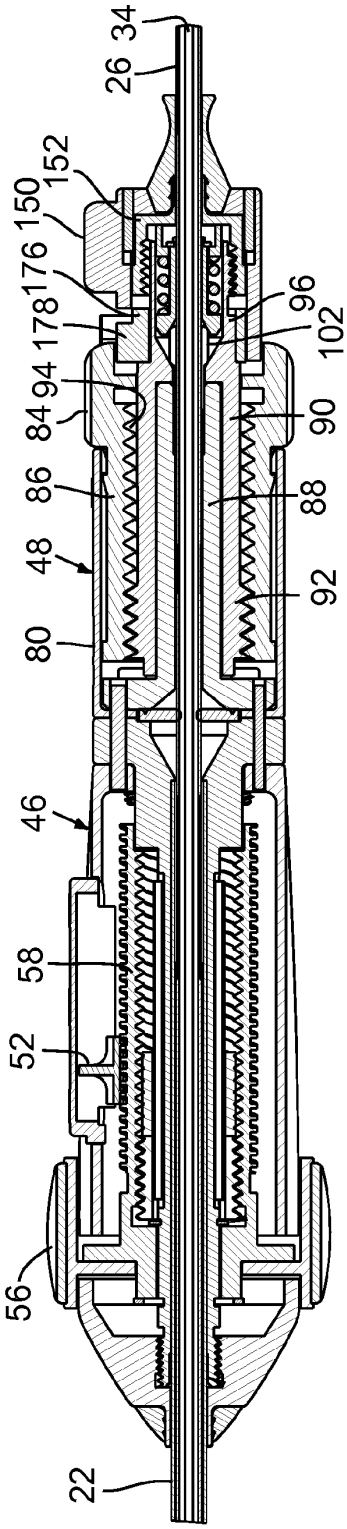

34
26
152
150
176
178
96
102
94
84
86
48
80
90
88
92
46
58
52
56
22

FIG. 21

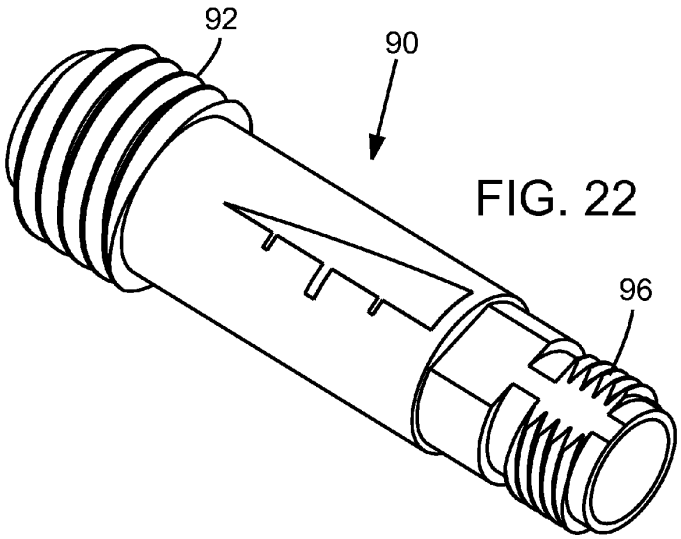


FIG. 22

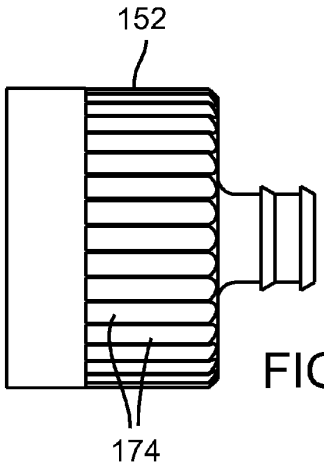


FIG. 23

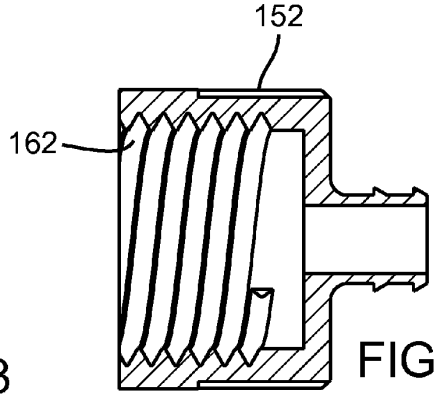


FIG. 24

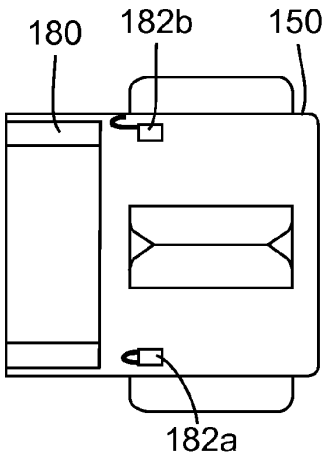


FIG. 25

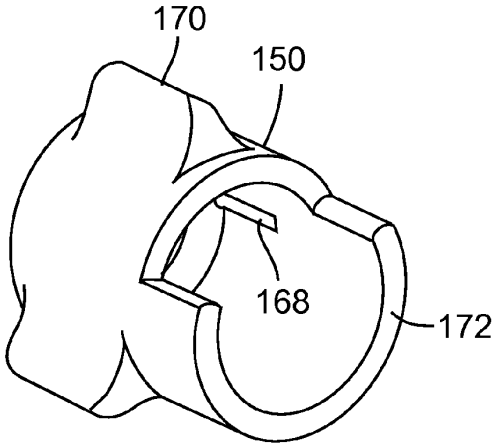


FIG. 26

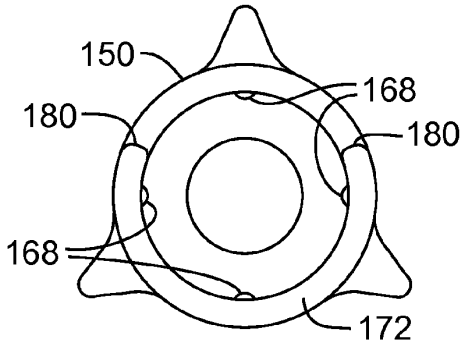


FIG. 27

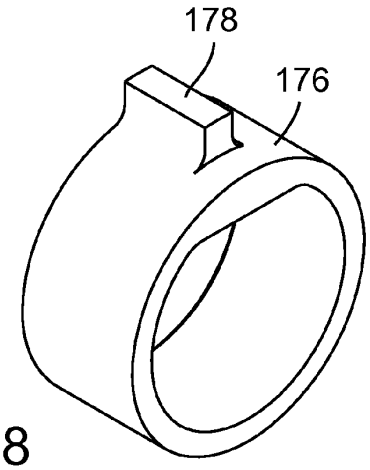


FIG. 28

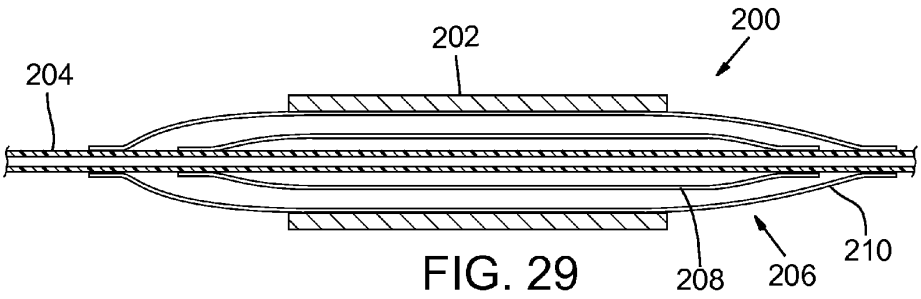


FIG. 29

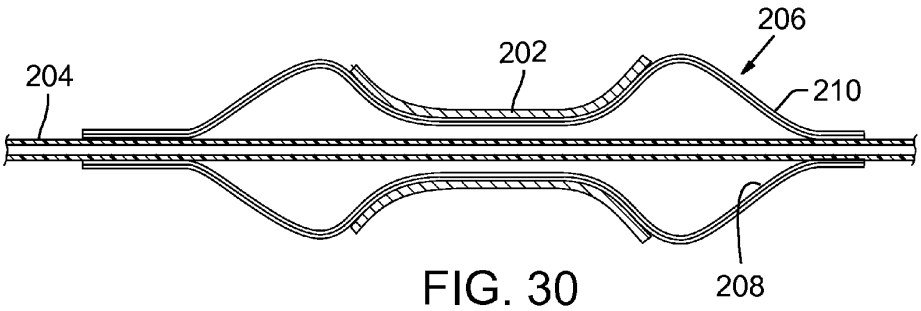


FIG. 30

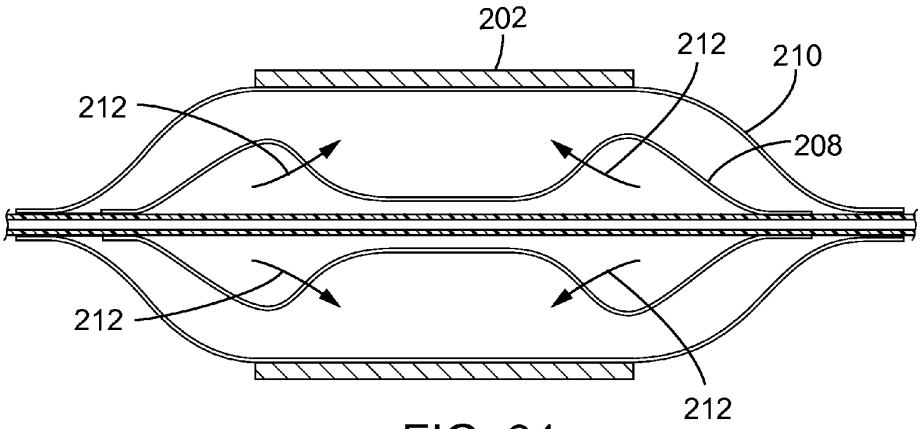


FIG. 31

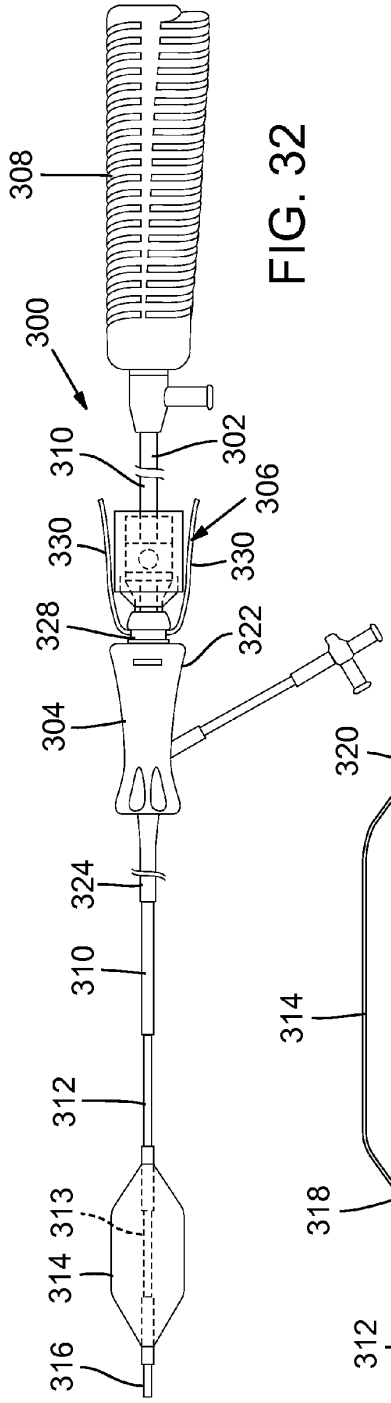


FIG. 32

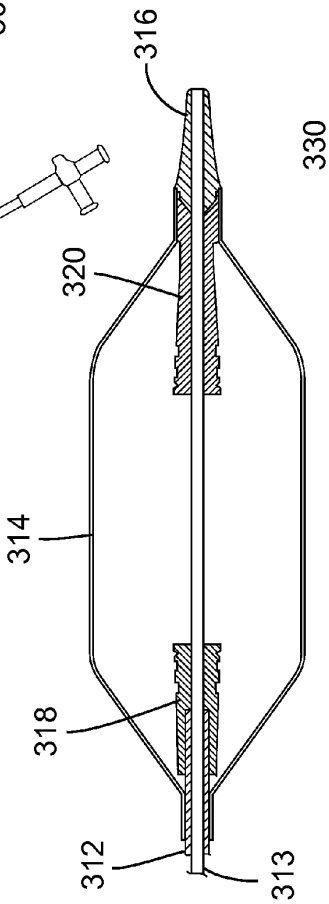


FIG. 33

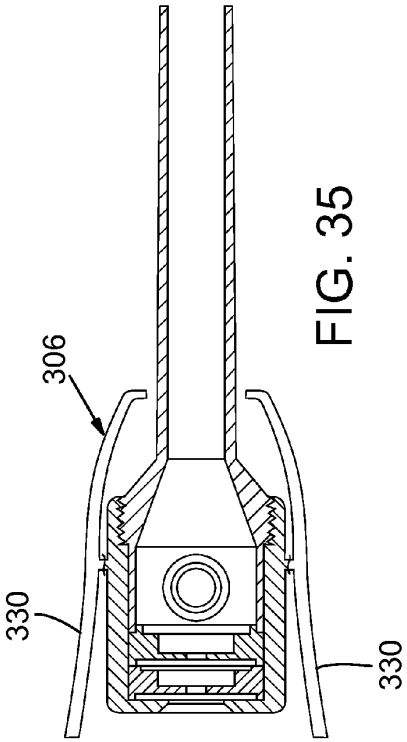


FIG. 35

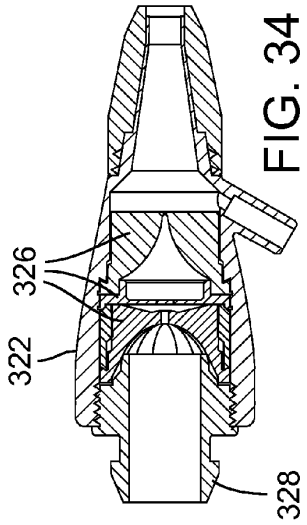


FIG. 34

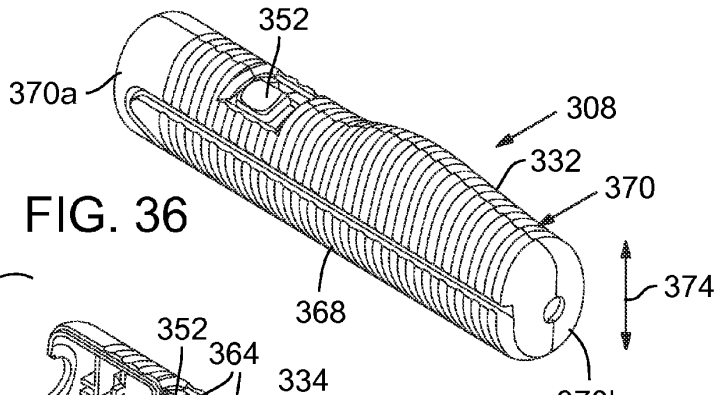


FIG. 36

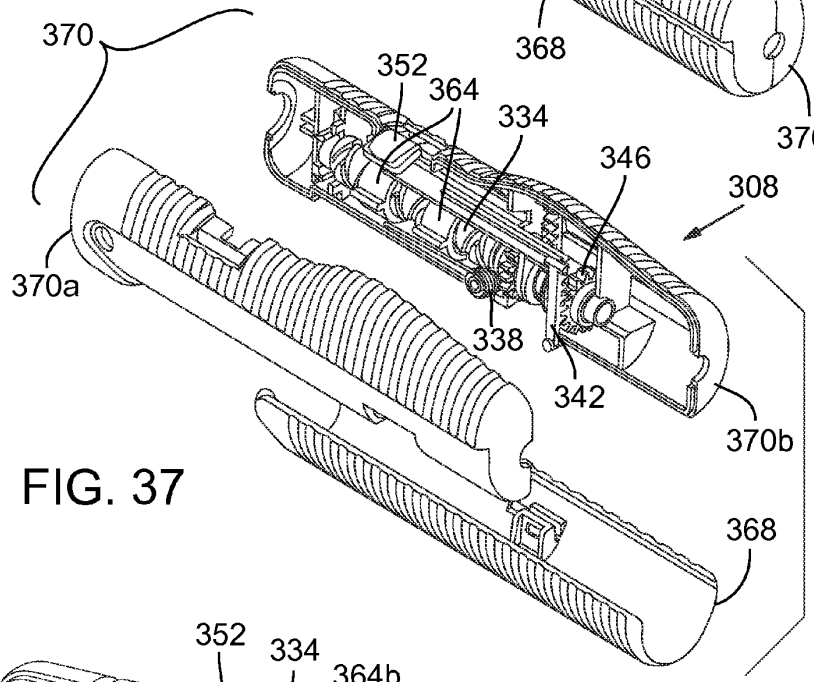


FIG. 37

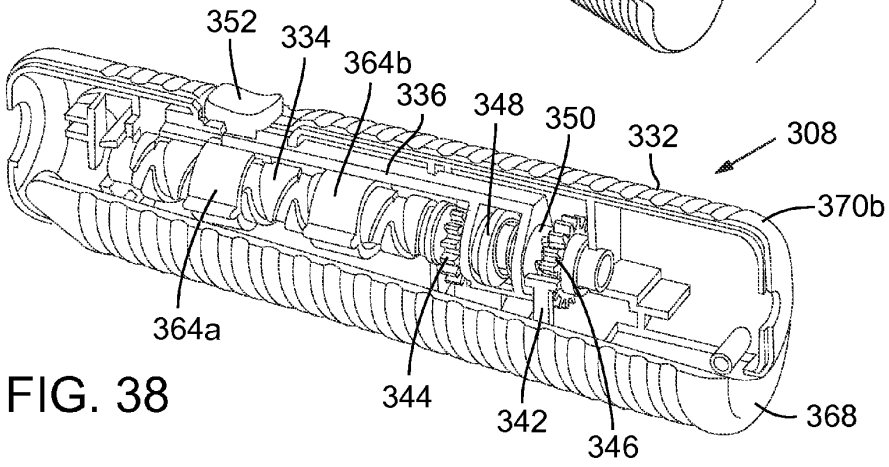


FIG. 38

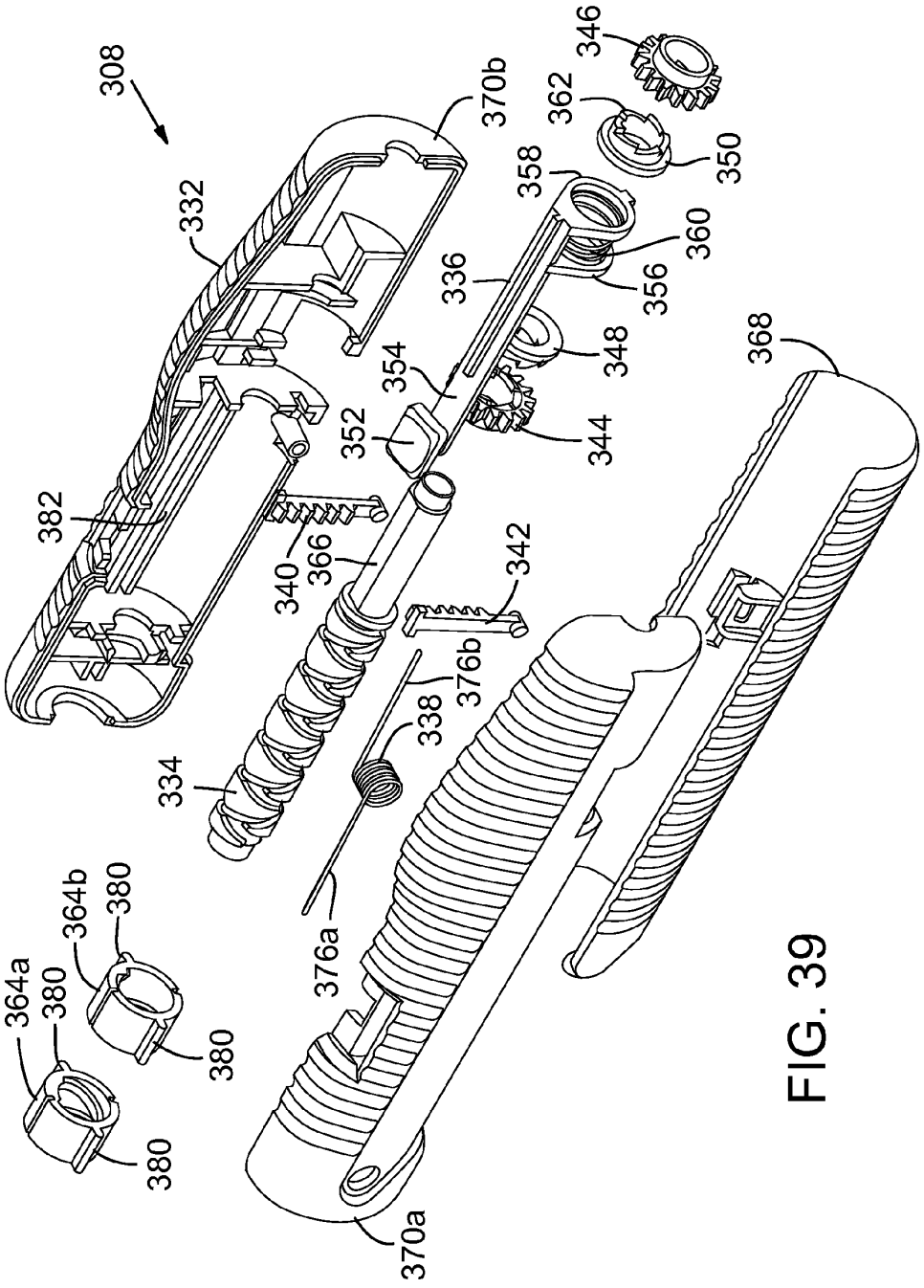
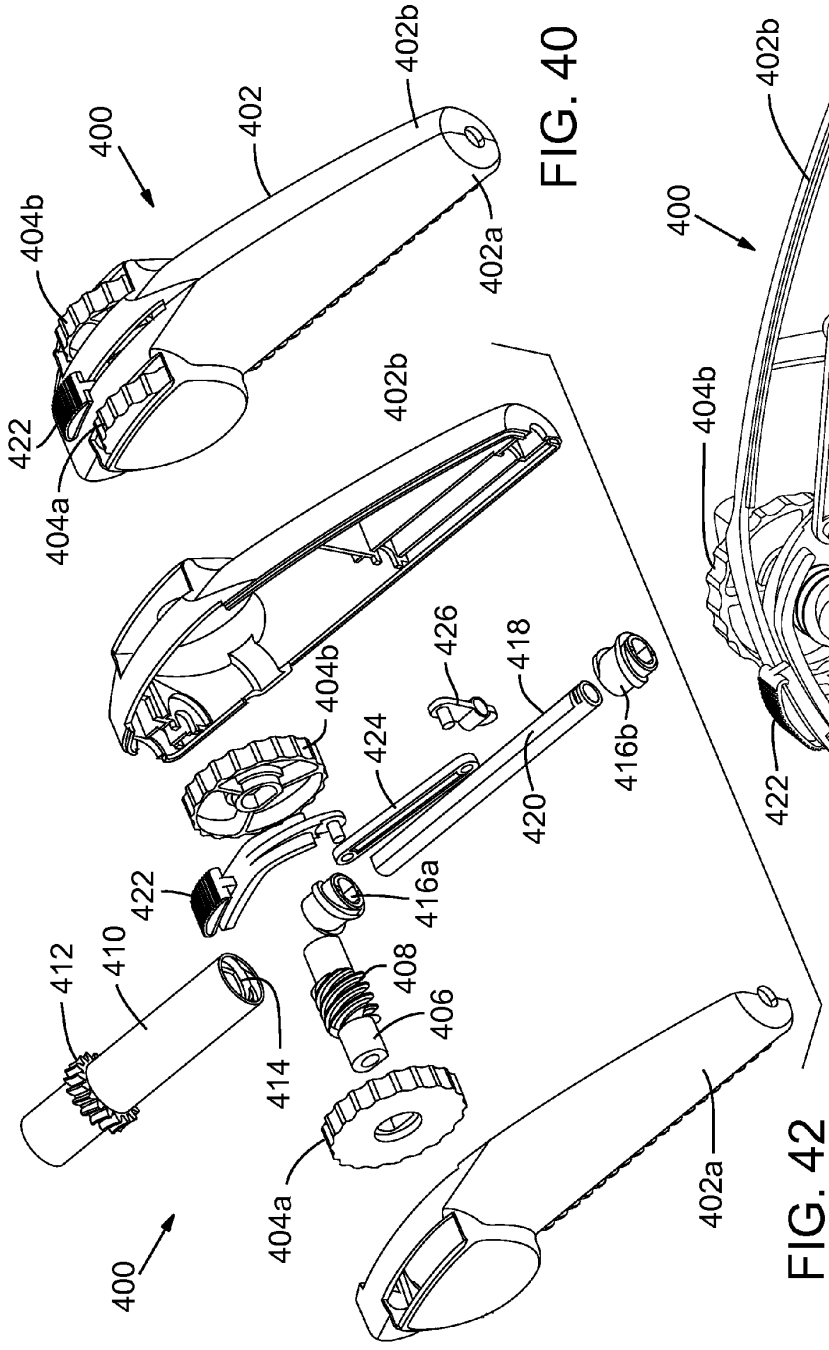

308
370b
346
362
350
358
332
360
336
356
348
354
368
352
344
382
366
342
340
376b
338
334
364b
380
364a
380
380
380
376a
370a

FIG. 39


400
402
402b
402a
404b
404a
422
FIG. 40
400
402b
404b
416b
416a
406
422
FIG. 41
402b
404b
426
418
424
420
416b
416a
422
412
410
408
406
414
404a
400
402a
FIG. 42

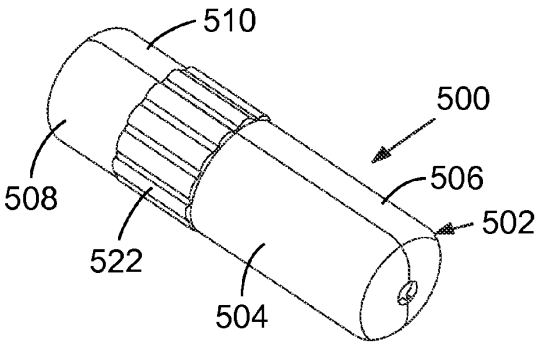


FIG. 43

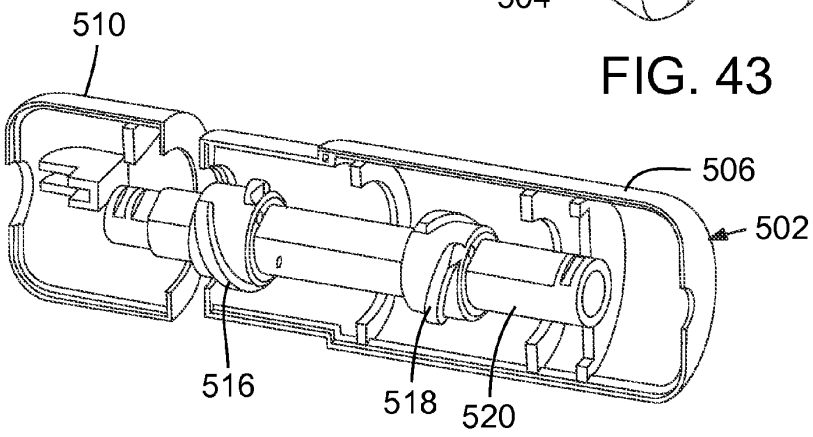


FIG. 44

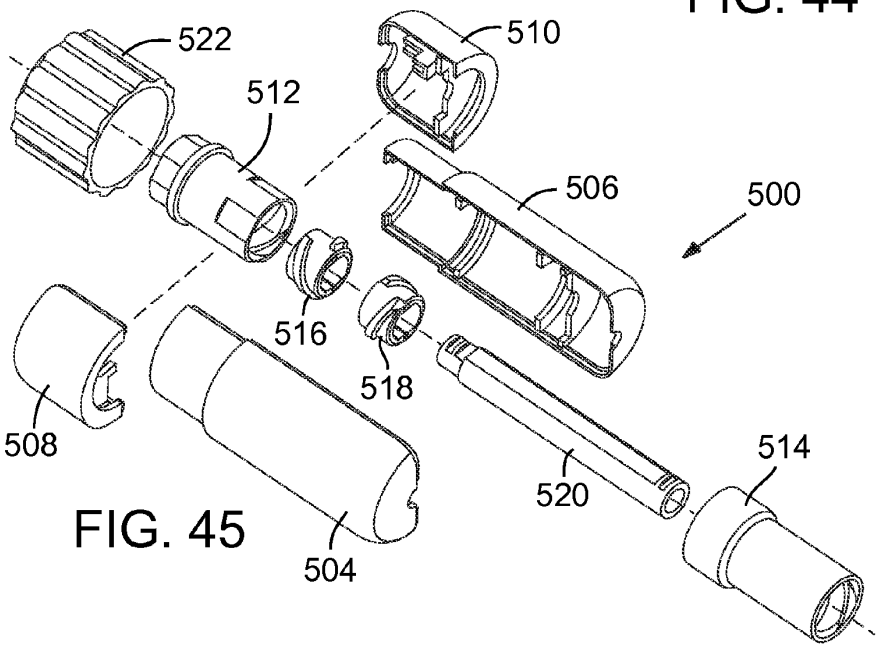


FIG. 45

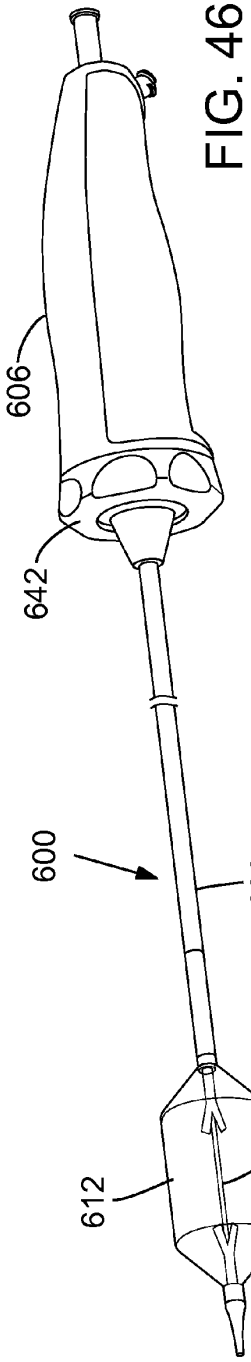


FIG. 46

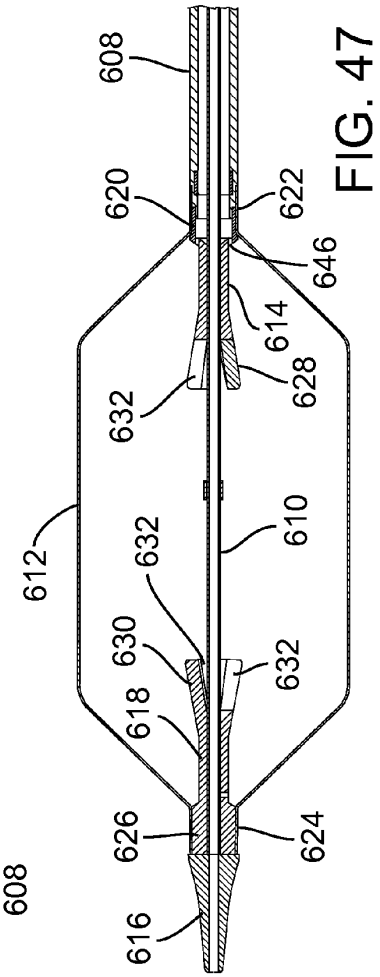


FIG. 47

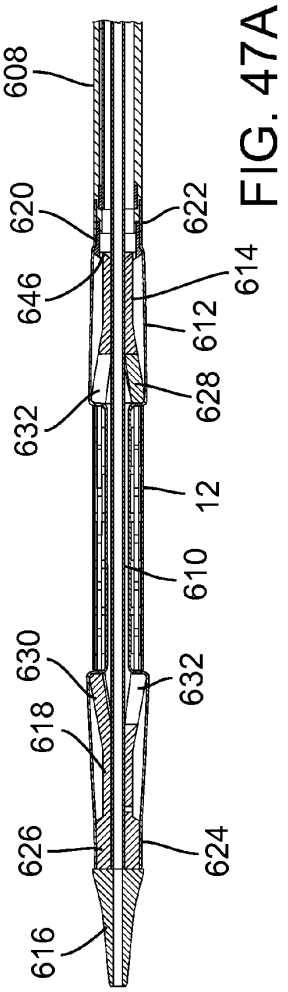


FIG. 47A

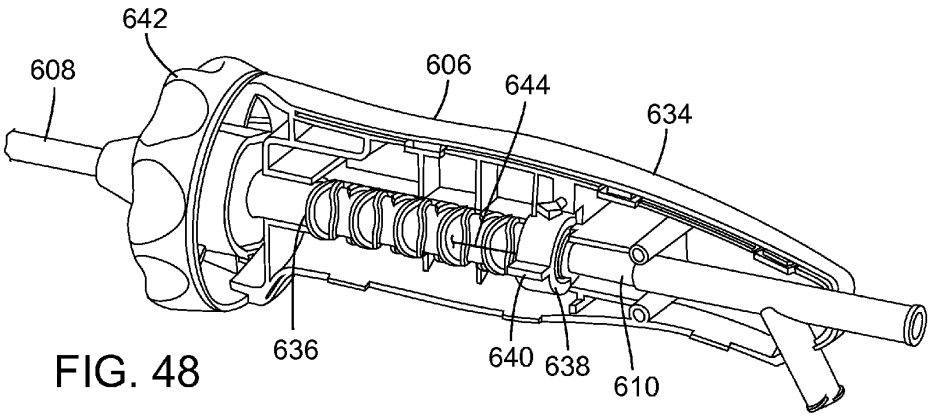


FIG. 48

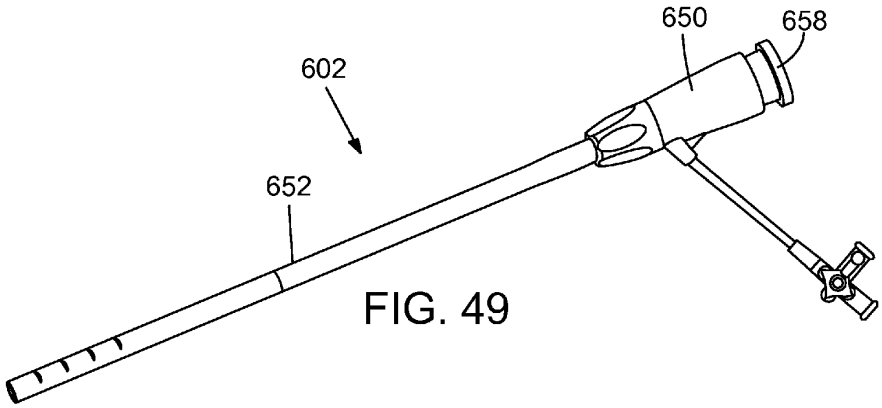


FIG. 49

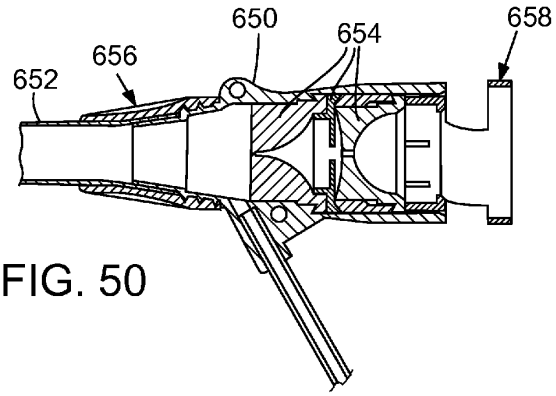


FIG. 50

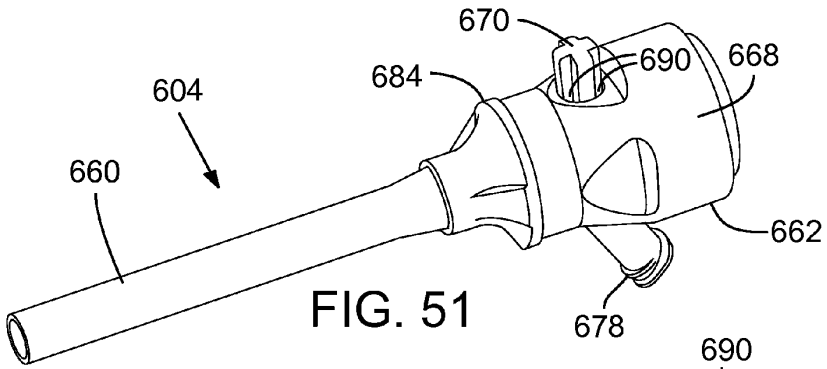


FIG. 51

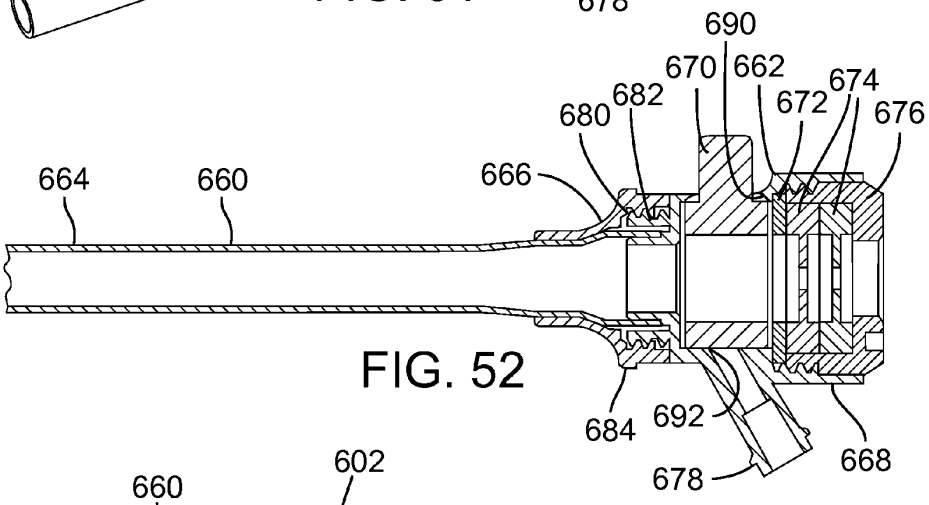


FIG. 52

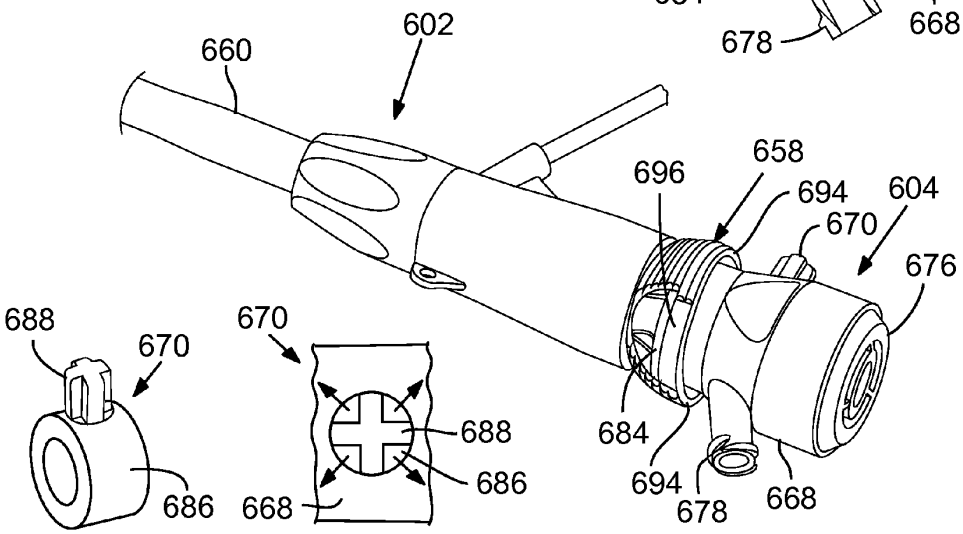


FIG. 53

FIG. 54

FIG. 55

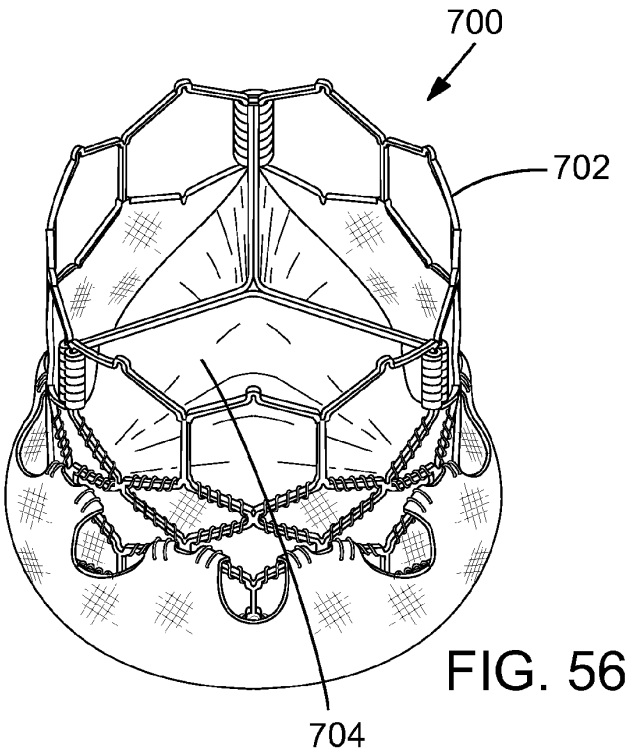


FIG. 56

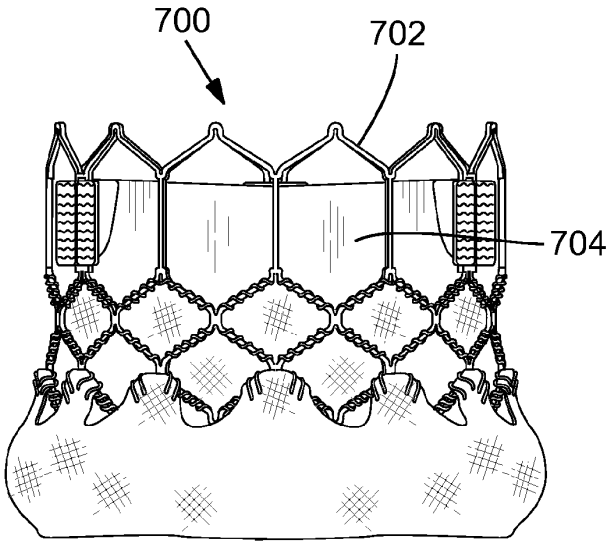


FIG. 57

DELIVERY SYSTEMS FOR PROSTHETIC HEART VALVE

CROSS REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Application No. 61/512,328, filed Jul. 27, 2011, which is incorporated herein by reference.

FIELD

The present disclosure concerns embodiments of delivery systems for implanting prosthetic heart valves.

BACKGROUND

Prosthetic cardiac valves have been used for many years to treat cardiac valvular disorders. The native heart valves (such as the aortic, pulmonary and mitral valves) serve critical functions in assuring the forward flow of an adequate supply of blood through the cardiovascular system. These heart valves can be rendered less effective by congenital, inflammatory or infectious conditions. Such damage to the valves can result in serious cardiovascular compromise or death. For many years the definitive treatment for such disorders was the surgical repair or replacement of the valve during open heart surgery, but such surgeries are prone to many complications. More recently a transvascular technique has been developed for introducing and implanting a prosthetic heart valve using a flexible catheter in a manner that is less invasive than open heart surgery.

In this technique, a prosthetic valve is mounted in a crimped state on the end portion of a flexible catheter and advanced through a blood vessel of the patient until the prosthetic valve reaches the implantation site. The prosthetic valve at the catheter tip is then expanded to its functional size at the site of the defective native valve such as by inflating a balloon on which the prosthetic valve is mounted. Alternatively, the prosthetic valve can have a resilient, self-expanding stent or frame that expands the prosthetic valve to its functional size when it is advanced from a delivery sheath at the distal end of the catheter.

A prosthetic valve that has a relatively large profile or diameter in the compressed state can inhibit the physician's ability to advance the prosthetic valve through the femoral artery or vein. More particularly, a smaller profile allows for treatment of a wider population of patients, with enhanced safety. Thus, a need exists for delivery devices that can minimize the overall crimp profile of the prosthetic valve for the delivery of the prosthetic valve through the patient's vasculature.

Relatively long delivery devices, such as used for transfemoral delivery of a prosthetic valve, can inhibit the physician's ability to position the prosthetic valve precisely at the desired implantation site because the forces applied to the handle at one end of the delivery device can cause unwanted movement of the prosthetic valve at the opposite end of the delivery device. Thus, a need exists for delivery devices that allow a physician to accurately control the positioning of the prosthetic valve at the desired implantation location.

When introducing a delivery device into the body, an introducer sheath typically is inserted first and then the delivery device is inserted through the introducer sheath and into the body. If the prosthetic valve is mounted on a balloon catheter, the prosthetic valve can contact the inner surface of the introducer sheath and may become dislodged from its preferred location on the balloon catheter, depending on the size of the crimped valve. Thus, a need exists for delivery devices that can better retain the crimped valve at its desired location on the balloon catheter as it is advanced through an introducer sheath.

SUMMARY

Described herein are systems and methods for delivering prosthetic devices, such as prosthetic heart valves, through the body and into the heart for implantation therein. The prosthetic devices delivered with the delivery systems disclosed herein are, for example, radially expandable from a radially compressed state mounted on the delivery system to a radially expanded state for implantation using an inflatable balloon (or equivalent expansion device) of the delivery system. Exemplary delivery routes through the body and into the heart include transfemoral routes, transapical routes, and transaortic routes, among others. Although the devices and methods disclosed herein are particular suited for implanting prosthetic heart valves (e.g., a prosthetic aortic valve or prosthetic mitral valve), the disclosed devices and methods can be adapted for implanting other types of prosthetic valves within the body (e.g., prosthetic venous valves) or other types of expandable prosthetic devices adapted to be implanted in various body lumens.

In some embodiments, a delivery apparatus for implanting a prosthetic, transcatheter heart valve via a patient's vasculature includes an adjustment device for adjusting the position of a balloon relative to a crimped prosthetic valve (and/or vice versa). A balloon catheter can extend coaxially with a guide (or flex) catheter, and a balloon member at the distal end of the balloon catheter can be positioned proximal or distal to a crimped prosthetic valve. The balloon member and the crimped prosthetic valve can enter the vasculature of a patient through an introducer sheath and, once the balloon member and the crimped prosthetic valve reach a suitable location in the body, the relative position of the prosthetic valve and balloon member can be adjusted so that the balloon member is positioned within the frame of the prosthetic valve so that the prosthetic valve eventually can be expanded at the treatment site. Once the crimped prosthetic valve is positioned on the balloon, the prosthetic valve is advanced to the vicinity of the deployment location (i.e., the native aortic valve) and the adjustment device can further be used to accurately adjust or "fine tune" the position of the prosthetic valve relative to the desired deployment location.

An exemplary method of implanting a radially compressible and expandable prosthetic device (e.g., a prosthetic heart valve) in the heart comprises: (a) introducing a delivery device into the body of a patient, the delivery device comprising a handle portion, an elongated shaft extending from the handle portion, the shaft having a distal end portion mounting an inflatable balloon and a prosthetic heart valve in a radially compressed state; (b) advancing the distal end portion of the delivery device toward the native heart valve until the prosthetic valve is within or adjacent the annulus of the native heart valve; (c) positioning the prosthetic heart valve at a desired implantation position within the annulus of the native by rotating an adjustment device coupled to the handle portion and the shaft to cause the shaft and the prosthetic valve to move distally and/or proximally relative to the handle portion until the prosthetic heart valve is at the desired implantation position; and (d) after the prosthetic heart valve has been moved to the desired implantation position, inflating the balloon to cause the prosthetic heart valve to radially expand and engage the annulus of the native heart valve.

An exemplary delivery apparatus for implantation of a prosthetic device (e.g., a prosthetic heart valve) in the heart comprises an elongated shaft comprising a proximal end portion and a distal end portion, an inflatable balloon, and a valve mounting member. The balloon is mounted on the distal end portion of the shaft. The valve mounting member is disposed on the distal end portion of the shaft within the balloon and is configured to facilitate frictional engagement between the prosthetic heart valve and the balloon when the prosthetic heart valve is mounted in a radially compressed state on the balloon and surrounding the mounting member. The mounting member comprises at least one longitudinally extending fluid passageway though which an inflation fluid in the balloon can flow.

In some embodiments, the at least one fluid passageway has first and second openings adjacent first and second ends of the prosthetic heart valve, respectively. When the prosthetic valve is mounted on the balloon in a crimped state, the inflation fluid in the balloon can flow from a first region of the balloon proximal to the first end of the prosthetic valve, inwardly through the first opening, through the fluid passageway, outwardly through the second opening and into a second region of the balloon distal to the second end of the prosthetic valve.

Another exemplary delivery apparatus for implantation of a prosthetic device (e.g., a prosthetic heart valve) in the heart comprises a handle portion and an elongated shaft extending from the handle portion. The shaft comprises a proximal end portion coupled to the handle portion and a distal end portion configured to mount a prosthetic heart valve in a radially compressed state. The apparatus also comprises a sliding member disposed on the proximal end portion of the shaft. The handle portion comprising a rotatable member that is operatively coupled to the sliding member so as to cause translational movement of the sliding member upon rotation of the rotatable member. A shaft engagement member is disposed on the shaft and couples the shaft to the sliding member. The shaft engagement member is configured to be manipulated between a first state and a second state. In the first state, the shaft can move freely in the longitudinal direction relative to the sliding member and the rotatable member. In the second state, the shaft engagement member frictionally engages the shaft and prevents rotational and longitudinal movement of the shaft relative to the sliding member such that rotation of the rotatable member causes corresponding longitudinal movement of the sliding member and the shaft. When a prosthetic device is mounted on the distal end of the shaft and the shaft engagement member is manipulated to engage the shaft, the rotatable member can be used to adjust the location of the prosthetic device relative to its desired implantation location within the heart.

In some embodiments, the shaft engagement member comprises a collet disposed on the shaft. The collet can have flexible fingers that can be forced to frictionally engage and retain the shaft relative to the sliding member so that the rotatable member can be used to adjust the position of the prosthetic device mounted on the distal end portion of the shaft.

Another exemplary delivery device for implantation of a prosthetic device (e.g., a prosthetic heart valve) within the heart, such as via a transapical or transaortic route, comprises an inflatable balloon, a proximal stop, and a distal stop. The stops are configured to limit longitudinal movement of the prosthetic device relative to the balloon while the prosthetic device is mounted over the balloon in the radially compressed state between the proximal stop and the distal stop. The proximal stop and the distal stop each comprise an end portion positioned within the balloon and configured to be positioned adjacent the prosthetic device when the prosthetic device is radially compressed between the proximal and distal stops. Each of the stop end portions comprises at least one longitudinally extending slot that allows the respective stop end portion to be radially compressed to a smaller diameter. The at least one longitudinally extending slot in each stop end portion can also be configured to allow a balloon-inflation fluid to flow radially through the respective stop and into the region of the balloon extending through the prosthetic valve.

In some embodiments, when a prosthetic device is mounted on the delivery device in the radially compressed state, the proximal stop and the distal stop are configured to allow a balloon-inflation fluid to flow from a proximal portion of the balloon, through the at least one slot in the proximal stop, through an intermediate portion of the balloon positioned within the prosthetic device, through the at least one slot in the distal stop, and into a distal portion of the balloon.

In some embodiments, a proximal end of the balloon is attached to the proximal stop and a distal end of the balloon is attached to the distal stop.

In some embodiments, the delivery device further comprises an outer shaft having a lumen and an inner shaft extending through the lumen of the outer shaft, with the proximal stop attached to a distal end of the outer shaft and positioned around the inner shaft and the distal stop attached to an outer surface of the inner shaft.

In some embodiments, the proximal stop further comprises a proximal portion attached to the distal end of the outer shaft and to a proximal end of the balloon, and an intermediate portion extending between the proximal portion and the end portion, the intermediate portion having an outer diameter that is less than an outer diameter of the proximal portion and less than the diameter of the end portion.

In some embodiments, the proximal stop is attached to the distal end of the outer shaft and further comprises at least one fluid passageway that allows an inflation fluid to flow through the at least one passageway and into the balloon.

In some embodiments, the distal stop further comprises a distal portion attached to a distal end of the balloon and an intermediate portion extending between the distal portion and the end portion, the intermediate portion having an outer diameter that is less than an outer diameter of the distal portion and less than the diameter of the end portion.

In some embodiments, the end portion of each stop decreases in diameter in a direction extending away from the prosthetic device.

In some embodiments, the delivery device further comprises a nosecone attached to a distal end of the distal stop.

In some embodiments, at least one of the stop end portions comprises at least three longitudinal slots that allow the stop end portion to be radially compressed to a smaller diameter when the prosthetic device is crimped onto the delivery device.

An exemplary method of implanting a prosthetic heart valve within the heart comprises: (a) introducing a distal end portion of a delivery device into the native aortic valve of the heart, a distal end portion of the delivery device comprising an inflatable balloon, a proximal stop and a distal stop positioned at least partially within the balloon, and a radially expandable prosthetic heart valve mounted over the balloon and between the proximal stop and the distal stop in a radially compressed state; (b) inflating the balloon to radially expand the prosthetic heart valve within the native aortic valve, wherein the balloon is inflated with an inflation fluid that

flows radially through the proximal and distal stops; (c) deflating the balloon; and (d) retracting the delivery device from the heart.

In some embodiments, the proximal stop is positioned adjacent to a proximal end of the prosthetic heart valve and the distal stop is positioned adjacent to a distal end of the prosthetic heart valve, such that the prosthetic device is longitudinally contained between the proximal and distal stops during introduction of the prosthetic heart valve through an introducer sheath into the body.

In some embodiments, inflating the balloon comprises causing the inflation fluid to flow: (i) through a first passageway in the proximal stop and into a proximal portion of the balloon; (ii) from the proximal portion of the balloon, through a second passageway in the proximal stop, and into an intermediate portion of the balloon within the prosthetic device; and (iii) from the intermediate portion of the balloon, through a passageway in the distal stop, and into a distal portion of the balloon.

In some embodiments, prior to introducing the delivery device into the heart, the prosthetic heart valve is crimped to the radially compressed state onto delivery device while the proximal stop and the distal stop are simultaneously radially compressed. The prosthetic heart valve can have a first outer diameter in the radially compressed state and the proximal stop and distal stop can be compressed from a second outer diameter to about the first outer diameter during the crimping. When compressive pressure is released after the crimping, the proximal stop and distal stop can be configured to resiliently expand from about the first outer diameter to about the second outer diameter.

An exemplary system for delivering a prosthetic device into a patient comprises an introducer sheath configured to be inserted partially into a patient, a loader configured to be inserted into a proximal end the introducer sheath, and a delivery device configured to be passed through the loader and the introducer sheath into the patient carrying a prosthetic device to be implanted in the patient. The loader comprises a flush port for selectively introducing fluid into the loader and a bleed port for selectively releasing fluid from within the loader, and both the flush port and the bleed port are sealed with the same resiliently flexible annular sealing member. The sealing member can comprise a push tab that extends radially through the bleed port, such that the bleed port is configured to be selectively opened by depressing the push tab in the radially inward direction.

The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a side view of a delivery apparatus for implanting a prosthetic heart valve, according to one embodiment.

FIG. **2**A is a cross-sectional view of the handle of the delivery apparatus of FIG. **1**.

FIG. **2**B is another cross-sectional view of the handle of the delivery apparatus of FIG. **1**.

FIG. **3** is side view of a section of the handle and a section of the distal end portion of the delivery apparatus of FIG. **1**.

FIG. **4** is a side view of the distal end portion of the delivery apparatus of FIG. **1**.

FIG. **5** is a side view of the distal end portion of the delivery apparatus of FIG. **1** showing the balloon in an inflated state.

FIG. **6** is an enlarged perspective view of a collet used in the handle of the delivery apparatus of FIG. **1**.

FIG. **7** is a cross-sectional view of the collet of FIG. **6**.

FIG. **8** is an enlarged side view of a mounting member for a prosthetic heart valve.

FIGS. **9-11** are enlarged, cross-sectional views of the distal end portion of the delivery apparatus of FIG. **1**, showing the inflation of a balloon for deployment of a prosthetic heart valve on the balloon.

FIG. **12** is a perspective view of an alternative embodiment of a mounting member for a prosthetic heart valve.

FIG. **13** is a side view of the mounting member of FIG. **12** shown partially in section.

FIG. **14** is an end view of the mounting member of FIG. **12**.

FIGS. **15-17** are enlarged, cross-sectional views of the distal end portion of a delivery apparatus containing the mounting member of FIG. **12**, and showing the inflation of a balloon for deployment of a prosthetic heart valve on the balloon.

FIG. **18** is an exploded perspective view of the handle of a delivery apparatus, according to another embodiment.

FIG. **19** is an enlarged perspective view of the collet, pusher element, spring, ring, and washer of the handle shown in FIG. **18**.

FIG. **20** is a cross-sectional view of the handle of the delivery apparatus of FIG. **18**.

FIG. **21** is another cross-sectional view of the handle of the delivery apparatus of FIG. **18**.

FIG. **22** is a perspective view of the inner shaft, or slider, of the handle shown in FIG. **18**.

FIG. **23** is an enlarged side view of the inner nut of the handle shown in FIG. **18**.

FIG. **24** is an enlarged cross-sectional view of the inner nut shown in FIG. **23**.

FIGS. **25-27** are enlarged top, perspective and end views, respectively, of the rotatable knob of the handle shown in FIG. **18**.

FIG. **28** is an enlarged perspective view of the indicator ring of the handle shown in FIG. **18**.

FIGS. **29-31** are cross-sectional views of the distal end portion of a delivery apparatus for a prosthetic heart valve, according to another embodiment, having two inflatable balloons for deploying a prosthetic valve.

FIG. **32** is a side view of a delivery apparatus for a prosthetic heart valve, an introducer, and a loader device, according to another embodiment.

FIG. **33** is an enlarged, cross-sectional view of the distal end portion of the delivery apparatus of FIG. **32**.

FIG. **34** is a cross-sectional view of the introducer of FIG. **32**.

FIG. **35** is a cross-sectional view of the loader of FIG. **32**.

FIG. **36** is a perspective view of the handle of the delivery apparatus shown in FIG. **32**.

FIG. **37** is a partially exploded, perspective view of the handle of FIG. **36**.

FIG. **38** is a perspective view of the handle of FIG. **36**, shown with a portion of the outer housing cut away for purposes of illustration.

FIG. **39** is an exploded, perspective view of the handle of FIG. **36**.

FIG. **40** is a perspective view of another embodiment of a handle that can be used in the delivery apparatus of FIG. **32**.

FIG. **41** is a perspective of the handle of FIG. **40**, with a portion of the outer housing and some internal components removed for purposes of illustration.

FIG. **42** is an exploded, perspective view of the handle of FIG. **40**.

FIG. **43** is a perspective view of another embodiment of a handle that can be used in the delivery apparatus of FIG. **32**.

FIG. **44** is a perspective of the handle of FIG. **43**, with a portion of the outer housing and some internal components removed for purposes of illustration.

FIG. **45** is an exploded, perspective view of the handle of FIG. **43**.

FIG. **46** is a perspective view of a delivery apparatus for a prosthetic heart valve, according to another embodiment.

FIG. **47** is an enlarged, cross-sectional view of the distal end portion of the delivery apparatus of FIG. **46**.

FIG. **47**A is an enlarged, cross-sectional view of the distal end portion of the delivery apparatus of FIG. **46** showing a prosthetic heart valve mounted in a crimped state on the balloon of the delivery apparatus.

FIG. **48** is a perspective view of the handle of the delivery apparatus of FIG. **46**, with a portion of the outer housing removed for purposes of illustration.

FIG. **49** is a perspective view of an introducer, according to another embodiment.

FIG. **50** is an enlarged, cross-sectional view of the proximal housing portion of the introducer shown in FIG. **49**.

FIG. **51** is a perspective view of a loader, according to another embodiment.

FIG. **52** is a cross-sectional view of the loader shown in FIG. **51**.

FIG. **53** is a perspective view of the loader of FIG. **51** shown inserted into the introducer of FIG. **49**.

FIG. **54** is a perspective view of the button valve of the loader shown in FIG. **51**.

FIG. **55** is a top plan view of the button valve shown in FIG. **51**.

FIG. **56** is a perspective view of a prosthetic heart valve, according to one embodiment.

FIG. **57** is a side elevation view of the prosthetic heart valve of FIG. **56**.

DETAILED DESCRIPTION

In particular embodiments, a delivery apparatus for implanting a prosthetic, transcatheter heart valve via a patient's vasculature includes an adjustment device for adjusting the position of a balloon relative to a crimped prosthetic valve (and/or vice versa). A balloon catheter can extend coaxially with a guide (or flex) catheter, and a balloon member at the distal end of the balloon catheter can be positioned proximal or distal to a crimped prosthetic valve. As described below in more detail, the balloon member and the crimped prosthetic valve can enter the vasculature of a patient through an introducer sheath and, once the balloon member and the crimped prosthetic valve reach a suitable location in the body, the relative position of the prosthetic valve and balloon member can be adjusted so that the balloon member is positioned within the frame of the prosthetic valve so that the prosthetic valve eventually can be expanded at the treatment site. Once the crimped prosthetic valve is positioned on the balloon, the prosthetic valve is advanced to the vicinity of the deployment location (i.e., the native aortic valve) and the adjustment device can further be used to accurately adjust or "fine tune" the position of the prosthetic valve relative to the desired deployment location.

FIG. **1** shows a delivery apparatus **10** adapted to deliver a prosthetic heart valve **12** (shown schematically in FIGS. **9-11**) (e.g., a prosthetic aortic valve) to a heart, according to one embodiment. The apparatus **10** generally includes a steerable guide catheter **14** (FIG. **3**), and a balloon catheter **16** extending through the guide catheter **14**. The guide catheter can also be referred to as a flex catheter or a main catheter. The use of the term main catheter should be understood, however, to include flex or guide catheters, as well as other catheters that do not have the ability to flex or guide through a patient's vasculature.

The guide catheter **14** and the balloon catheter **16** in the illustrated embodiment are adapted to slide longitudinally relative to each other to facilitate delivery and positioning of prosthetic valve **12** at an implantation site in a patient's body, as described in detail below.

The guide catheter **14** includes a handle portion **20** and an elongated guide tube, or shaft, **22** extending from handle portion **20** (FIG. **3**). FIG. **1** shows the delivery apparatus without the guide catheter shaft **22** for purposes of illustration. FIG. **3** shows the guide catheter shaft **22** extending from the handle portion **20** over the balloon catheter. The balloon catheter **16** includes a proximal portion **24** (FIG. **1**) adjacent handle portion **20** and an elongated shaft **26** that extends from the proximal portion **24** and through handle portion **20** and guide tube **22**. The handle portion **20** can include a side arm **27** having an internal passage which fluidly communicates with a lumen defined by the handle portion **20**.

An inflatable balloon **28** is mounted at the distal end of balloon catheter **16**. As shown in FIG. **4**, the delivery apparatus **10** is configured to mount the prosthetic valve **12** in a crimped state proximal to the balloon **28** for insertion of the delivery apparatus and prosthetic valve into a patient's vasculature, which is described in detail in U.S. Publication No. 2009/0281619 (U.S. application Ser. No. 12/247,846, filed Oct. 8, 2008), which is incorporated herein by reference. Because prosthetic valve **12** is crimped at a location different from the location of balloon **28** (e.g., in this case prosthetic valve **12** desirably is crimped proximal to balloon **28**), prosthetic valve **12** can be crimped to a lower profile than would be possible if prosthetic valve **12** was crimped on top of balloon **28**. This lower profile permits the surgeon to more easily navigate the delivery apparatus (including crimped valve **12**) through a patient's vasculature to the treatment location. The lower profile of the crimped prosthetic valve is particularly helpful when navigating through portions of the patient's vasculature which are particularly narrow, such as the iliac artery. The lower profile also allows for treatment of a wider population of patients, with enhanced safety.

A nose piece **32** (FIG. **4**) can be mounted at the distal end of the delivery apparatus **10** to facilitate advancement of the delivery apparatus **10** through the patient's vasculature to the implantation site. In some instances, it may be useful to have nose piece **32** connected to a separate elongated shaft so that nose piece **32** can move independently of other elements of delivery apparatus **10**. Nose piece **32** can be formed of a variety of materials, including various plastic materials.

As can be seen in FIG. **5**, the balloon catheter **16** in the illustrated configuration further includes an inner shaft **34** (FIG. **2**A) that extends from proximal portion **24** and coaxially through the outer balloon catheter shaft **26** and the balloon **28**. The balloon **28** can be supported on a distal end portion of inner shaft **34** that extends outwardly from the outer shaft **26** with a proximal end portion **36** of the balloon secured to the distal end of outer shaft **26** (e.g., with a suitable adhesive) (FIG. **5**). The outer diameter of inner shaft **34** is sized such that an annular space is defined between the inner and outer shafts along the entire length of the outer shaft. The proximal portion **24** of the balloon catheter can be formed with a fluid passageway (not shown) that is fluidly connectable to a fluid source (e.g., saline) for inflating the balloon. The fluid passageway is in fluid communication with the annular space between inner shaft **34** and outer shaft **26** such that fluid from the fluid source can flow through fluid pas-

sageway, through the space between the shafts, and into balloon **28** to inflate the same and deploy prosthetic valve **12**.

The proximal portion **24** also defines an inner lumen that is in communication with a lumen **38** of the inner shaft **34** that is sized to receive guide wire (not shown) that can extend coaxially through the inner shaft **34** and the nose cone **32**.

The inner shaft **34** and outer shaft **26** of the balloon catheter can be formed from any of various suitable materials, such as nylon, braided stainless steel wires, or a polyether block amide (commercially available as Pebax®). The shafts **26**, **34** can have longitudinal sections formed from different materials in order to vary the flexibility of the shafts along their lengths. The inner shaft **34** can have an inner liner or layer formed of Teflon® to minimize sliding friction with a guide wire.

The distal end portion of the guide catheter shaft **22** comprises a steerable section **68** (FIG. **3**), the curvature of which can be adjusted by the operator to assist in guiding the apparatus through the patient's vasculature, and in particular, the aortic arch. The handle **20** in the illustrated embodiment comprises a distal handle portion **46** and a proximal handle portion **48**. The distal handle portion **46** functions as a mechanism for adjusting the curvature of the distal end portion of the guide catheter shaft **22** and as a flex indicating device that allows a user to measure the relative amount of flex of the distal end of the guide catheter shaft **22**. In addition, the flex indicating device provides a visual and tactile response at the handle the device, which provides a surgeon with an immediate and direct way to determine the amount of flex of the distal end of the catheter.

The distal handle portion **46** can be operatively connected to the steerable section **68** and functions as an adjustment mechanism to permit operator adjustment of the curvature of the steerable section via manual adjustment of the handle portion. Explaining further, the handle portion **46** comprises a flex activating member **50**, an indicator pin **52**, and a cylindrical main body, or housing **54**. As shown in FIGS. **2**A and **2**B, the flex activating member **50** comprises an adjustment knob **56** and a shaft **58** extending proximally from the knob into the housing **54**. A proximal end portion of the guide catheter shaft **22** extends into and is fixed within the central lumen of the housing **54**. An inner sleeve **70** surrounds a portion of the guide catheter shaft **22** inside the housing **54**. A threaded slide nut **72** is disposed on and is slidable relative to the sleeve **70**. The slide nut **72** is formed with external threads that mate with internal threads **60** of the shaft **58**.

The slide nut **72** can be formed with two slots formed on the inner surface of the nut and extending the length thereof. The sleeve **70** can be formed with longitudinally extending slots that are aligned with the slots of the slide nut **72** when the slide nut is placed on the sleeve. Disposed in each slot is a respective elongated nut guide, which can be in the form of an elongated rod or pin **76**. The nut guides **76** extend radially into respective slots in the slide nut **72** to prevent rotation of the slide nut **72** relative to the sleeve **70**. By virtue of this arrangement, rotation of the adjustment knob **56** (either clockwise or counterclockwise) causes the slide nut **72** to move longitudinally relative to the sleeve **70** in the directions indicated by double-headed arrow **74**.

One or more pull wires **78** (FIG. **2**A) couple the adjustment knob **56** to the steerable section **68** to adjust the curvature of the steerable section upon rotation of the adjustment knob. For example, the proximal end portion of the pull wire **78** can extend into and can be secured to a retaining pin, such as by crimping the pin around the proximal end of the pull wire, which pin is disposed in a slot in the slide nut **72**. The pull wire extends from the pin, through the slot in the slide nut, a slot in the sleeve **70**, and into and through a pull wire lumen in the shaft **22**. The distal end portion of the pull wire is secured to the distal end portion of the steerable section **68**.

The pin, which retains the proximal end of the pull wire **78**, is captured in the slot in the slide nut **72**. Hence, when the adjustment knob **56** is rotated to move the slide nut **72** in the proximal direction, the pull wire also is moved in the proximal direction. The pull wire pulls the distal end of the steerable section **68** back toward the handle portion, thereby bending the steerable section and reducing its radius of curvature. The friction between the adjustment knob **56** and the slide nut **72** is sufficient to hold the pull wire taut, thus preserving the shape of the bend in the steerable section if the operator releases the adjustment knob **56**. When the adjustment knob **56** is rotated in the opposite direction to move the slide nut **72** in the distal direction, tension in the pull wire is released. The resiliency of the steerable section **68** causes the steerable to return its normal, non-deflected shape as tension on the pull wire is decreased. Because the pull wire is not fixedly secured to the slide nut **72** (the pin can move within the slot in the nut), movement of the slide nut in the distal direction does not push on the end of the pull wire, causing it to buckle. Instead, the pin is allowed to float within the slot of the slide nut **72** when the knob **56** is adjusted to reduce tension in the pull wire, preventing buckling of the pull wire.

In particular embodiments, the steerable section **68** in its non-deflected shape is slightly curved and in its fully curved position, the steerable section generally conforms to the shape of the aortic arch. In other embodiments, the steerable section can be substantially straight in its non-deflected position.

The distal handle portion **46** can have other configurations that are adapted to adjust the curvature of the steerable section **68**. One such alternative handle configuration is shown in co-pending U.S. patent application Ser. No. 11/152,288 (published under Publication No. US2007/0005131), which is incorporated herein by reference in its entirety. Additional details relating to the steerable section and handle configuration discussed above can be found in U.S. patent application Ser. No. 11/852,977 (published as U.S. Publication No. US2008/0065011), which is incorporated herein by reference in its entirety.

The shaft **58** also includes an externally threaded surface portion **62**. As shown in FIG. **2**B, a base portion **64** of the indicator pin **52** mates with the externally threaded surface portion **62** of the shaft **58**. The shaft **58** extends into the main body **54** and the indicator pin **52** is trapped between the externally threaded surface portion **62** and the main body **54**, with a portion of the indicator pin **52** extending into a longitudinal slot **66** of the handle. As the knob **56** rotated to increase the curvature of the distal end of the guide catheter shaft **22**, the indicator pin **52** tracks the external threaded portion **62** of the flex activating member and moves in the proximal direction inside of the slot **66**. The greater the amount of rotation of the knob **56**, the further indicator pin **52** moves towards the proximal end of the proximal handle portion **46**. Conversely, rotating the knob **56** in the opposite direction decreases the curvature of the distal end of the guide catheter shaft **22** (i.e., straightens the guide catheter shaft) and causes corresponding movement of the indicator pin **52** toward the distal end of the distal handle portion **46**.

The outer surface of the main body **54** of the distal handle portion **46** can include visual indicia adjacent the slot **66** that indicate the amount of flex of the distal end of the guide catheter shaft **22**, based on the position of the indicator pin **52** relative to the visual indicia. Such indicia can identify the amount of flex in any of a variety of manners. For example,

the outer surface of the main body **54** can include a series of numbers (e.g., 0 to 10) adjacent the slot that indicate the amount of curvature of the guide catheter shaft **22** based on the position of the indicator pin **52** relative to the number scale.

As described above, when the delivery apparatus is introduced into the vasculature of the patient, a crimped prosthetic valve **12** is positioned proximal to the balloon **28** (FIG. **4**). Prior to expansion of the balloon **28** and deployment of prosthetic valve **12** at the treatment site, the prosthetic valve **12** is moved relative to the balloon (or vice versa) to position the crimped prosthetic valve on the balloon for deploying (expanding) the prosthetic valve. As discussed below, the proximal handle portion **48** serves as an adjustment device that can be used to move the balloon **28** proximally into position within the frame of prosthetic valve **12**, and further to accurately position the balloon and the prosthetic valve at the desired deployment location.

As shown in FIGS. **2**A and **2**B, the proximal handle portion **48** comprises an outer housing **80** and an adjustment mechanism **82**. The adjustment mechanism **82**, which is configured to adjust the axial position of the balloon catheter shaft **26** relative to the guide catheter shaft **22**, comprises an adjustment knob **84** and a shaft **86** extending distally into the housing **80**. Mounted within the housing **80** on the balloon catheter shaft **26** is an inner support **88**, which in turn mounts an inner shaft **90** (also referred to as a slider or sliding mechanism) (also shown in FIG. **22**). The inner shaft **90** has a distal end portion **92** formed with external threads that mate with internal threads **94** that extend along the inner surface of the adjustment mechanism **82**. The inner shaft **90** further includes a proximal end portion **96** that mounts a securement mechanism **98**, which is configured to retain the position of the balloon catheter shaft **26** relative to the proximal handle portion **48** for use of the adjustment mechanism **82**, as further described below. The inner shaft **90** can be coupled to the inner support **88** such that rotation of shaft **86** causes the inner shaft **90** to move axially within the handle. For example, the inner support **88** can have an axially extending rod or rail that extends into slot formed in the inner surface of the inner shaft **90**. The rod or rail prevents rotation of the inner shaft **90** but allows it to move axially upon rotation of the shaft **86**.

The securement mechanism **98** includes internal threads that mate with external threads of the proximal end portion **96** of the inner shaft. Mounted within the proximal end portion **96** on the balloon catheter shaft **26** is a pusher element **100** and a shaft engagement member in the form of a collet **102**. The collet **102** is configured to be manipulated by the securement mechanism between a first state in which collet allows the balloon catheter shaft to be moved freely in the longitudinal and rotational directions and a second state in which the collet frictionally engages the balloon catheter shaft and prevents rotational and longitudinal movement of the balloon catheter shaft relative to the inner shaft **90**, as further described below.

As best shown in FIGS. **6** and **7**, the collet **102** comprises a distal end portion **104**, an enlarged proximal end portion **106**, and a lumen **108** that receives the balloon catheter shaft **26**. A plurality of axially extending, circumferentially spaced slots **110** extend from the proximal end of the collet to a location on the distal end portion **104**, thereby forming a plurality of flexible fingers **112**. The proximal end portion can be formed with a tapered end surface **114** that engages a corresponding tapered end surface of the pusher element **100** (FIG. **2**A).

As noted above, the securement mechanism **98** is operable to restrain movement of the balloon catheter shaft **26** (in the axial and rotational directions) relative to the proximal handle portion **48**. Explaining further, the securement mechanism **98** is movable between a proximal position (shown in FIGS. **2**A and **2**B) and a distal position closer to the adjacent end of the knob **84**. In the proximal position, the collet **102** applies little, if any, force against the balloon catheter shaft **26**, which can slide freely relative to the collet **102**, the entire handle **20**, and the guide catheter shaft **22**. When the securement mechanism **98** is rotated so as to move to its distal position closer to knob **84**, the securement mechanism urges pusher element **100** against the proximal end of the collet **102**. The tapered surface of the pusher element pushes against the corresponding tapered surface **114** of the collet, forcing fingers **112** radially inward against the outer surface of the balloon catheter shaft **26**. The holding force of the collet **102** against the balloon catheter shaft locks the balloon catheter shaft relative to the inner shaft **90**. In the locked position, rotation of the adjustment knob **84** causes the inner shaft **90** and the balloon catheter shaft **26** to move axially relative to the guide catheter shaft **22** (either in the proximal or distal direction, depending on the direction the knob **84** is rotated).

The adjustment knob **84** can be utilized to position the prosthetic valve **12** on the balloon **28** and/or once the prosthetic valve **12** is on the balloon, to position the prosthetic valve and the balloon at the desired deployment site within the native valve annulus. One specific method for implanting the prosthetic valve **12** in the native aortic valve is as follows. The prosthetic valve **12** initially can be crimped on a mounting region **120** (FIGS. **4** and **5**) of the balloon catheter shaft **26** immediately adjacent the proximal end of the balloon **28** or slightly overlapping the proximal end of the balloon. The proximal end of the prosthetic valve can abut the distal end **122** of the guide catheter shaft **22** (FIG. **4**), which keeps the prosthetic valve in place on the balloon catheter shaft as the delivery apparatus and prosthetic valve are inserted through an introducer sheath. The prosthetic valve **12** can be delivered in a transfemoral procedure by first inserting an introducer sheath into the femoral artery and pushing the delivery apparatus through the introducer sheath into the patient's vasculature.

After the prosthetic valve **12** is advanced through the narrowest portions of the patient's vasculature (e.g., the iliac artery), the prosthetic valve **12** can be moved onto the balloon **28**. For example, a convenient location for moving the prosthetic valve onto the balloon is the descending aorta. The prosthetic valve can be moved onto the balloon, for example, by holding the handle portion **46** steady (which retains the guide catheter shaft **22** in place), and moving the balloon catheter shaft **26** in the proximal direction relative to the guide catheter shaft **22**. As the balloon catheter shaft is moved in the proximal direction, the distal end **122** of the guide catheter shaft pushes against the prosthetic valve, allowing the balloon **28** to be moved proximally through the prosthetic valve in order to center the prosthetic valve on the balloon, as depicted in FIG. **9**. The balloon catheter shaft can include one or more radiopaque markers to assist the user in positioning the prosthetic valve at the desired location on the balloon. The balloon catheter shaft **26** can be moved in the proximal direction by simply sliding/pulling the balloon catheter shaft in the proximal direction if the securement mechanism **98** is not engaged to retain the shaft **26**. For more precise control of the shaft **26**, the securement mechanism **98** can be engaged to retain the shaft **26**, in which case the adjustment knob **84** is rotated to effect movement of the shaft **26** and the balloon **28**.

As shown in FIG. **5**, the delivery apparatus can further include a mounting member **124** secured to the outer surface of the shaft **34** within the balloon **28**. The mounting member helps retain the prosthetic valve in place on the balloon by

facilitating the frictional engagement between the prosthetic valve and the outer surface of the balloon. The mounting member **124** helps retain the prosthetic valve in place for final positioning of the prosthetic valve at the deployment location, especially when crossing the native leaflets, which typically are calcified and provide resistance against movement of the prosthetic valve. The nose cone **32** can include a proximal portion **126** inside the balloon to assist in positioning the prosthetic valve. The proximal portion **126** desirably comprises a tapered member that has a maximum diameter at its proximal end adjacent the distal end of the prosthetic valve (FIG. **9**) and tapers in a direction toward the distal end of the nosecone **32**. The tapered member **126** serves as a transition section between the nosecone and the prosthetic valve as the prosthetic valve is pushed through the calcified native leaflets by shielding the distal end of the prosthetic valve from contacting the native leaflets. Although FIG. **9** shows the prosthetic valve having a crimped diameter slightly larger than the diameter of the tapered member **126** at its proximal end, the tapered member **126** can have a diameter at its proximal end that is the same as or slightly larger than the diameter of the crimped prosthetic valve, or at least the same as or slightly larger than the diameter of the metal frame of the crimped prosthetic valve.

As shown in FIG. **9**, the prosthetic valve desirably is positioned on the balloon for deployment such that the distal end of the prosthetic valve is slightly spaced from the nose cone portion **126**. When the prosthetic valve is positioned as shown in FIG. **9**, the guide catheter shaft **22** can be moved proximally relative to the balloon catheter shaft **26** so that the guide catheter shaft is not covering the inflatable portion of the balloon **28**, and therefore will not interfere with inflation of the balloon.

As the prosthetic valve **12** is guided through the aortic arch and into the ascending aorta, the curvature of the steerable section **68** can be adjusted (as explained in detail above) to help guide or steer the prosthetic valve through that portion of the vasculature. As the prosthetic valve is moved closer toward the deployment location within the aortic annulus, it becomes increasingly more difficult to control the precise location of the prosthetic valve by pushing or pulling the handle portion **20** due to the curved section of the delivery apparatus. When pushing or pulling the handle portion **20**, slack is removed from the curved section of the delivery apparatus before the pushing/pulling force is transferred to the distal end of the delivery apparatus. Consequently, the prosthetic valve tends to "jump" or move abruptly, making precise positioning of the prosthetic valve difficult.

For more accurate positioning of the prosthetic valve within the aortic annulus, the prosthetic valve **12** is placed as close as possible to its final deployment location (e.g., within the aortic annulus such that an inflow end portion of the prosthetic valve is in the left ventricle and an outflow end portion of the prosthetic valve is in the aorta) by pushing/pulling the handle **20**, and final positioning of the prosthetic valve is accomplished using the adjustment knob **84**. To use the adjustment knob **84**, the securement mechanism **98** is placed in its locked position, as described above. Then, the handle **20** is held steady (which retains the guide catheter shaft **22** in place) while rotating the adjustment knob **84** to move the balloon catheter shaft **26**, and thus the prosthetic valve, in the distal or proximal directions. For example, rotating the knob in a first direction (e.g., clockwise), moves the prosthetic valve proximally into the aorta, while rotating the knob in a second, opposite direction (e.g., counterclockwise) advances the prosthetic valve distally toward the left ventricle. Advantageously, operation of the adjustment knob **84** is effective to move the prosthetic valve in a precise and controlled manner without sudden, abrupt movements as can happen when pushing or pulling the delivery apparatus for final positioning.

When the prosthetic valve is at the deployment location, the balloon **28** is inflated to expand the prosthetic valve **12** (as depicted in FIG. **11**) so as to contact the native annulus. The expanded prosthetic valve becomes anchored within the native aortic annulus by the radial outward force of the valve's frame against the surrounding tissue.

The mounting member **124** within the balloon is configured to allow the inflation fluid (e.g., saline) to flow unobstructed from the proximal end of the balloon to the distal end of the balloon. As best shown in FIG. **8**, for example, the mounting member **124** comprises a coiled wire (e.g., a metal coil) having a first section **124***a*, a second section **124***b*, a third section **124***c*, a fourth section **124***d*, and a fifth section **124***e*. When the prosthetic valve **12** is positioned on the balloon for deployment, the second section **124***b* is immediately adjacent the proximal end of the prosthetic valve and the fourth section **124***d* is immediately adjacent the distal end of the prosthetic valve. The first and fifth sections **124***a*, **124***e*, respectively, which are at the proximal and distal ends of the mounting member, respectively, are secured to the balloon catheter shaft. The second, third, and fourth sections **124***b*, **124***c*, and **124***d*, respectively, are relatively larger in diameter than the first and fifth sections and are spaced radially from the outer surface of the balloon catheter shaft. As can be seen, the second section **124***b* and the fourth section **124***d* are formed with spaces between adjacent coils. The third section can be formed with smaller spaces (or no spaces) between adjacent coils to maximize the surface area available to retain the prosthetic valve on the balloon during final positioning of the prosthetic valve at the deployment location.

Referring to FIG. **10**, the spacing between coils of the second and fourth sections **124***b*, **124***d* allows the inflation fluid to flow radially inwardly through the coils of the second section **124***b*, axially through the lumen of the third section **124***c*, radially outwardly through the coils of the fourth section **124***d*, into the distal section of the balloon, in the direction of arrows **128**. The nose cone portion **126** also can be formed with one or more slots **130** that allow the inflation fluid to flow more easily past the proximal nose cone portion **126** into the distal section of the balloon. In the illustrated embodiment, the proximal nose cone portion **126** has three circumferentially spaced slots **130**. Since the inflation fluid can pressurize and inflate the proximal and distal sections of the balloon at substantially the same rate, the balloon can be inflated more evenly for controlled, even expansion of the prosthetic valve.

FIGS. **12-14** illustrate a mounting member **140** according to another embodiment. The mounting member **140** comprises a cylindrical inner wall **142**, a cylindrical outer wall **144**, and a plurality of angularly spaced ribs **146** separating the inner and outer walls. The inner wall **142** is secured to the outer surface of the shaft **34** within the balloon. In particular embodiments, the mounting member **140** can be made of a relatively rigid material (e.g., polyurethane or another suitable plastic) that does not radially compress when the prosthetic valve is moved onto the balloon. As shown in FIG. **16**, during inflation of the balloon, inflation fluid in the proximal section of the balloon can flow through the spaces **148** between the inner and outer walls of the mounting member, through one or more slots **130** in the proximal nose cone portion **126**, and into the distal section of the balloon, in the direction of arrows **128**.

It should be noted that the location of the threaded portions of the adjustment mechanism **82** and the inner shaft **90** can be reversed. That is, adjustment mechanism **82** can have an externally threaded portion that engages an internally threaded portion of the inner shaft **90**. In addition, for embodiments where the balloon **28** is initially positioned proximal to the prosthetic valve **12**, the adjustment mechanism **82** can be used to move the balloon distally relative to the crimped prosthetic valve in order to center the prosthetic valve on the balloon for deployment.

FIGS. **56** and **57** show a prosthetic heart valve **700**, according to another embodiment. The heart valve **700** comprises a frame, or stent, **702** and a leaflet structure **704** supported by the frame. In particular embodiments, the heart valve **700** is adapted to be implanted in the native aortic valve and can be implanted in the body using, for example, the delivery apparatus **10** described above. The prosthetic valve **700** can also be implanted within the body using any of the other delivery apparatuses described herein. Thus, the frame **702** typically comprises a plastically expandable material, such as stainless steel, a nickel based alloy (e.g., a nickel-cobalt-chromium alloy), polymers, or combinations thereof. In other embodiments, the prosthetic valve **12**, **700** can be a self-expandable prosthetic valve with a frame made from a self-expanding material, such as Nitinol. When the prosthetic valve is a self-expanding valve, the balloon of the delivery apparatus can be replaced with a sheath or similar restraining device that retains the prosthetic valve in a radially compressed state for delivery through the body. When the prosthetic valve is at the implantation location, the prosthetic valve can be released from the sheath, and therefore allowed to expand to its functional size. It should be noted that any of the delivery apparatuses disclosed herein can be adapted for use with a self-expanding valve.

FIG. **18** is an exploded, perspective view of the distal end section of an alternative embodiment of a delivery device, indicated at **10'**. The delivery device **10'** shares many similarities with the delivery device **10**, and therefore components of the delivery device **10'** that are the same as those in the delivery device **10** are given the same reference numerals and are not described further. One difference between the delivery device **10** and the delivery device **10'** is that the latter includes a different mechanism for locking/securing the balloon catheter shaft **26** relative to the adjustment knob **84**.

Referring to FIGS. **18** and **19**, the locking mechanism for the balloon catheter shaft comprises an adjustment knob **150** housing an inner nut **152**, a washer **154** and a ring **156** disposed inside the inner nut **152**, a biasing member in the form of a coiled spring **158**, a pusher element **160**, and a shaft engagement member in the form of a collet **102**. As best shown in FIGS. **20** and **21**, the inner nut **152** includes inner threads **162** (FIG. **24**) that engage the external threads of the distal end portion **96** of the inner shaft **90** (FIG. **22**). The pusher element **160** includes a proximal shaft **164** and an enlarged distal end portion **166** that bears against the proximal end portion **106** of the collet **102**. The spring **158** is disposed on the shaft **164** of the pusher element **160** and has a proximal end that bears against the ring **156** and a distal end that bears against the distal end portion **166** of the pusher element **160**.

Referring to FIGS. **25-27**, the adjustment knob **150** is formed with a plurality of longitudinally extending, circumferentially spaced projections **168** on the inner surface of the knob. A distal portion of the knob **150** includes one or more radially extending projections **170** for gripping by a user and a proximal portion of the knob comprises a semi-annular portion **172**. The knob **150** extends co-axially over the inner nut **152** with the projections **168** mating with respective grooves **174** on the outer surface of the nut **152** such that rotation of the knob causes corresponding rotation of the nut **152**.

The delivery device **10'** can be used in the manner described above in connection with the delivery device **10** to deliver a prosthetic valve in the vicinity of the implantation site. To restrain movement of the balloon catheter shaft **26** for fine positioning of the prosthetic valve, the knob **150** is rotated, which in turn causes rotation of the inner nut **152**. The inner nut **152** is caused to translate in the distal direction along the external threads on the distal end portion **96** of the shaft **90**. As the nut **152** is moved distally, the nut **152** pushes against the ring **156**, which in turn pushes against the spring **158**. The spring **158** presses against the distal end portion **166** of the pusher element **160**, urging the pusher element against the collet **102**. The pushing force of the pusher element **160** against the collet causes the fingers **112** of the collet to frictionally engage the balloon catheter shaft **26**, thereby retaining the balloon catheter shaft relative to the inner shaft **90**. In the locked position, rotation of the adjustment knob **84** causes the inner shaft **90** and the balloon catheter shaft **26** to move axially relative to the guide catheter shaft **22** (either in the proximal or distal direction, depending on the direction the knob **84** is rotated).

The biasing force of the spring **158** desirably is sufficient to lock the collet against the balloon catheter shaft with a relatively small degree of rotation of the knob **150**, such as less than **360** degrees rotation of the knob. In the illustrated embodiment, the knob **150** is rotated less than **180** degrees from an unlocked position (in which the collet does not retain the balloon catheter shaft) to a locked position (in which the collet frictionally engages and retains the balloon catheter shaft). Conversely, rotating the knob **150** in the opposite direction from the locked position to the unlocked position through the same degree of rotation allows the spring **158** to release the biasing force against the pusher element and the collet so as to permit axial movement of the balloon catheter shaft relative to the collet.

As best shown in FIG. **21**, an indicator ring **176** is disposed on the shaft **90** adjacent the proximal end of the knob **84**. The indicator ring **176** sits within the semi-annular wall **172** of the knob **150** and includes an indicator tab **178** that extends into the annular space between the ends **180** (FIG. **27**) of the semi-annular wall **172**. As best shown in FIG. **25**, the outer surface of the knob **150** can include visual indicia that indicate whether the balloon catheter shaft **26** is in a locked state relative to the adjustment knob **84**. In the illustrated implementation, for example, a first indicia **182***a* is located adjacent one end **180** of the semi-annular wall **172** and a second indicia **182***b* is located adjacent the other end **180** of the semi-annular wall **172**. The first indicia **182***a* is a graphical representation of a closed lock (indicating that the balloon catheter shaft is in a locked state) and the second indicia **182***b* is a graphical representation of an open lock (indicating that the balloon catheter shaft is in an unlocked state). However, it should be understood that the indicia can take various other forms (text and/or graphics) to indicate the locked and unlocked states.

Since the indicator ring **176** is fixed rotationally relative to the knob **150**, the indicator tab **178** limits rotation of the knob **150** through an arc length defined by the annular space between the ends **180** of the semi-annular wall **172** (about 170 degrees in the illustrated embodiment). When the knob **150** is rotated in a first direction (counterclockwise in the illustrated example), the indicator tab **178** will contact the wall end **180** adjacent indicia **182***b* and prevent further rotation of the knob **150**. In this position, the collet **102** does not frictionally

engage the balloon catheter shaft **26**, which can be moved freely relative to the proximal handle portion **48**. When the knob **150** is rotated in a second direction (clockwise in the illustrated example), the indicator tab **178** will contact the wall end **180** adjacent indicia **182***a* and prevent further rotation of the knob **150**. In this position, the collet **102** is caused to frictionally engage the balloon catheter shaft in the manner described above to restrain axial and rotational movement of the balloon catheter shaft relative to the proximal handle portion **48**.

FIGS. **29-31** show the distal end portion of a balloon catheter **200**, according to another embodiment, that can be used to implant an intraluminal implant, such as a stent or a stented prosthetic valve. The features of the balloon catheter **200** can be implemented in the delivery apparatuses disclosed herein (e.g., apparatus **10** of FIG. **1**). In the figures, a prosthetic valve is shown schematically and is identified by reference numeral **202**. The balloon catheter **200** includes a balloon catheter shaft **204**. The proximal end of the shaft **204** is mounted to a handle (not shown) and the distal end of the shaft mounts a balloon assembly **206**.

The balloon assembly **206** comprises an inner balloon **208** disposed inside an outer balloon **210**. The inner balloon **208** is shaped to control expansion of the prosthetic valve **202** while the outer balloon is shaped to define the final expanded shape of the prosthetic valve. For example, as shown in FIG. **30**, the inner balloon **208** can have a "dog bone" shape when inflated, having bulbous end portions that taper inwardly to form a generally cylindrical center portion of a reduced diameter. The shape of the inner balloon **208** helps maintain the position of the prosthetic valve relative to the balloon as the prosthetic valve is expanded due to the larger end portions that restrict movement of the prosthetic valve in the axial directions. The distal end portion of the shaft **204** can have openings to allow an inflation fluid to flow from the lumen of the shaft **204** into the inner balloon **208**.

The inner balloon **208** can be formed with small pores or openings that are sized to permit suitable inflation of the inner balloon and allow the inflation fluid to flow outwardly into the space between the two balloons to inflate the outer balloon, as indicated by arrows **212**. After the inner balloon is inflated, which partially expands the prosthetic valve **202** (FIG. **30**), the inflation fluid begins inflating the outer balloon **210** (FIG. **31**). Inflation of the outer balloon further expands the prosthetic valve **202** to its final desired shape (e.g., cylindrical as shown in FIG. **31**) against the surrounding tissue. In such a two-stage expansion of the prosthetic valve **202**, the position of the prosthetic valve relative to the shaft **204** can be controlled due to the inner balloon, which limits axial movement of the prosthetic valve during its initial expansion.

In an alternative embodiment, in lieu of or in addition to the pores or holes in the inner balloon, the inner balloon can be configured to burst at a predetermined pressure (e.g., 1-5 bars) after it is inflated to a desired size. After the inner balloon ruptures, the inflation fluid can begin inflating the outer balloon.

FIG. **32** discloses a delivery system **300**, according to another embodiment, that can be used to implant an expandable prosthetic valve. The delivery system **300** is specifically adapted for use in introducing a prosthetic valve into a heart in a transapical procedure, which is disclosed in co-pending application Ser. No. 12/835,555, filed Jul. 13, 2010 (U.S. Publication No. 2011/0015729), which is incorporated herein by reference. In a transapical procedure, a prosthetic valve is introduced into the left ventricle through a surgical opening in the apex of the heart. The delivery system **300** similarly can be used for introducing a prosthetic valve into a heart in a transaortic procedure. In a transaortic procedure, a prosthetic valve is introduced into the aorta through a surgical incision in the ascending aorta, such as through a partial J-sternotomy or right parasternal mini-thoracotomy, and then advanced through the ascending aorta toward heart.

The delivery system comprises a balloon catheter **302**, an introducer **304**, and a loader **306**. The balloon catheter **302** comprises a handle **308**, an outer flush shaft **310** extending from the handle, an articulating main shaft **312** extending from the handle **308** coaxially through the outer shaft **310**, an inner shaft **313** extending from the handle coaxially through the articulating shaft **312**, an inflatable balloon **314** mounted on the shaft **312**, and a nose cone **316** mounted on the inner shaft **313** distal to the balloon.

As best shown in FIG. **33**, a pusher element, or stop member, **318** is mounted on the shaft **312** within the proximal portion of the balloon and the nose cone is formed with a stop member **320** that extends into the distal portion of the balloon. The spacing between the distal end of the pusher element **318** and the proximal end of the stop member **320** defines an annular space sized to partially receive a prosthetic valve that is crimped on the balloon. In use, the prosthetic valve is crimped onto the balloon between the pusher element **318** and the stop member **320** such that the proximal end of the prosthetic valve can abut the pusher element and the distal end of the prosthetic valve can abut the stop member (depicted in the embodiment shown in FIG. **47**A). In this manner, these two elements assist in retaining the position of the prosthetic valve on the balloon as it is inserted through the introducer **304**.

As shown in FIG. **32**, the introducer **304** comprises an introducer housing **322** and a distal sheath **324** extending from the housing **322**. The introducer **304** is used introduce or insert the balloon catheter **302** into a patient's body. As shown in FIG. **34**, the introducer housing **322** houses one or more valves **326** and includes a proximal cap **328** for mounting the loader. The loader **306** provides a coupling between the balloon catheter and the introducer. The loader **306** includes two retaining arms **330** that engage the proximal cap **328** of the introducer. The manner of using a loader to assist in inserting a balloon catheter and prosthetic valve into an introducer is described below with respect to the embodiment shown in FIGS. **51-53**.

The construction of the handle **308** is shown in FIGS. **36-39**. The handle **308** includes a housing **332**, which houses a mechanism for effecting controlled deflection, or articulation, of balloon catheter shaft **312**. The mechanism in the illustrated embodiment comprises a shaft **334**, a sliding mechanism **336**, a spring **338**, and proximal and distal rack gears **340**, **342**, respectively. The proximal end portion of the shaft **334** is formed with external threads that engage internal threads of two threaded nuts **364***a*, **364***b* inside the handle. The shaft **334** can rotate within the handle but is restricted from translational movement within the handle. The nuts **364** desirably have opposite threads and are disposed on respective portions of the shaft **334** that have corresponding external threads. For example, the proximal nut **364***a* can have left-handed threads and is disposed on left-handed threads on the shaft, while the distal nut **364***b* can have right-handed threads and is disposed on right-handed threads on the shaft. This causes the nuts **364** to translate in opposite directions along the threads of the shaft **334** upon its rotation. As best shown in FIG. **39**, each nut **364** has a pair of radially extending flanges **380** on diametrically opposite sides of the nut. The inside of the housing is formed with a pair of elongated slots **382** (one of which is shown in FIG. **39**) on opposing inside surfaces of the housing. The opposing flanges **380** on each nut **364** can extend into respective slots **382**, which prevent rotation of the

nuts upon rotation of the shaft **334**. In this manner, the nuts **364** are caused to move lengthwise of the shaft **334** upon its rotation.

The distal end portion of the shaft **334** supports a proximal spur gear **344**, a distal spur gear **346**, a proximal clutch **348**, and a distal clutch **350**. The shaft **334** has a flat **366** that engages corresponding flats on center bores of the clutches **348**, **350**, which provides for rotation of the shaft when one of the clutches is engaged and rotated by a respective spur gear, as described below. The sliding mechanism **336** includes a user-engageable actuator **352**, an elongate arm **354** extending from actuator **352**, and proximal and distal rings **356**, **358**, respectively, mounted on the distal end portion of the arm **354**. Mounted on the shaft **334** and held between the rings is a coil spring **360**.

Two pull wires (not shown) extend from the handle through the balloon catheter shaft **312** on diametrically opposite sides of the balloon catheter shaft to its distal end portion. A first pull wire has a proximal end secured to the proximal nut **364***a* inside the handle and a distal end that is secured to the distal end portion of the balloon catheter shaft **312**. A second pull wire has a proximal end secured to the distal nut **364***b* inside the handle and a distal end that is secured to the distal end portion of the balloon catheter shaft **312** on a diametrically opposite side from the securement location of the first pull wire.

The housing **332** is configured to actuate the deflection (articulation) mechanism inside the handle when it is squeezed by the hand of a user. For example, the housing **332** can comprise a lower housing section **368** and an upper housing section **370**, which can be comprised of two separable housing sections **370***a*, **370***b* for ease of assembly. Referring to FIG. **36**, the lower housing section **368** is mounted to the upper housing section **370** in a manner that permits the two sections to move toward and apart from each other a limited distance when squeezed by a user's hand, as indicated by arrow **374**. The torsion spring **338** has one arm **376***a* that bears against the inner surface of the upper housing portion **370** and another arm **376***b* that bears against the inner surface of the lower housing portion **368** to resiliently urge the two housing portions apart from each other. As such, squeezing the handle moves the upper and lower housing portions together and releasing manual pressure allows the housing portions to move apart from each other a limited amount under the spring force. In an alternative embodiment, a portion of the housing can be made of a flexible or deformable material that can deform when squeezed by the hand of a user in order to actuate the deflection mechanism.

The deflection mechanism works in the following manner. Squeezing the handle **332** causes the rack gears **340**, **342** to move in opposite directions perpendicular to shaft **334** (due to movement of the upper and lower housing sections), which in turn causes rotation of the corresponding spur gears **344**, **346** in opposite directions. The sliding mechanism **336** can be manually moved between a proximal position, a neutral (intermediate) position, and a distal position. When the sliding mechanism is in the neutral position (FIG. **36**), the clutches are disengaged from their respective spur gears, such that rotation of the spur gears does not rotate the shaft **334**. However, sliding the sliding mechanism **336** distally to a distal position pushes the coil spring **360** against the distal clutch **350** to engage the distal spur gear **346**. While the sliding mechanism is held in the distal position, the handle is squeezed and the resulting rotation of the distal spur gear **346** is transmitted to the shaft **334** to rotate in the same direction, which in turn causes the nuts **364** to move in opposite directions along the shaft **334** (e.g., toward each other). Translation of the nuts **364** in opposite directions applies tension to the first pull wire and introduces slack to the second pull wire, causing the balloon catheter shaft **312** to bend or deflect in a first direction. The face of the clutch **350** that engages spur gear **346** is formed with teeth **362** that cooperate with corresponding features of the gear to rotate the clutch and shaft **334** when the handle is squeezed, and allow the gear to spin or rotate relative to the clutch when manual pressure is removed from the handle. In this manner, the balloon catheter shaft bends a predetermined amount corresponding to each squeeze of the handle. The deflection of the balloon catheter shaft can be controlled by repeatedly squeezing the handle until the desired degree of deflection is achieved.

The balloon catheter shaft **312** can be deflected in a second direction, opposite the first direction by sliding the sliding mechanism **336** in the proximal direction, which pushes the coil spring **360** against the proximal clutch **348** to engage the proximal spur gear **344**. While holding the sliding mechanism in the proximal position and squeezing the handle, the proximal spur gear **344** rotates the proximal clutch **348** in the same direction. Rotation of the proximal clutch is transmitted to the shaft **334** to rotate in the same direction, resulting in translation of the nuts **364** in opposite directions (e.g., if the nuts move toward each other when the sliding mechanism is in the distal position, then the nuts move away from each other when the sliding mechanism is in the proximal position). The proximal clutch **348** is similarly formed with teeth **362** that engage the proximal spur gear **344** and cause rotation of the proximal clutch and shaft **334** only when the handle is squeezed but not when manually pressure is removed from the handle. In any case, movement of the threaded nuts **364** applies tension to the second pull wire and introduces slack to the first pull wire, causing the balloon catheter shaft **312** to bend in the opposite direction.

FIGS. **40-42** show an alternative embodiment of a handle, indicated at **400**, that can be incorporated in the balloon catheter **302** (in place of handle **308**). The handle **400** comprises a housing **402**, which can be formed from two halves **402***a*, **402***b* for ease of assembly. Two wheels, or rotatable knobs, **404***a*, **404***b* are positioned on opposite sides of the handle. The knobs are mounted on opposite ends of a shaft **406** having gear teeth **408**. A rotatable, hollow cylinder **410** extends lengthwise inside of the handle in a direction perpendicular to shaft **406**. The cylinder **410** includes external gear teeth **412** that engage the gear teeth **408** on shaft **406**. The inner surface of the cylinder **410** is formed with internal threads **414**, which can include right-handed and left-handed threads. A proximal threaded nut **416***a* and a distal threaded nut **416***b* are disposed inside of the cylinder **410** and are mounted for sliding movement on a rail **418** that extends co-axially through the cylinder. The nuts **416***a*, **416***b* have external threads that are threaded in opposite directions and engage the corresponding right-handed and left-handed threads on the inner surface of the cylinder **410**. The rail **418** has a flat **420** that engages corresponding flats on the inner bores of the nuts **416***a*, **416***b*, which allows the nuts to translate along the length of the rail without rotating.

First and second pull wires (not shown) are provided and secured to respective nuts **416***a*, **416***b* and the distal end of the balloon catheter shaft **312** as previously described. Deflection of the balloon catheter shaft **312** in first and second opposing directions can be accomplished by rotating the knobs **404***a*, **404***b* (which rotate together) clockwise and counterclockwise. For example, rotating the knobs clockwise produces rotation of the cylinder **410** via gear teeth **408** engaging gear teeth **412**. Rotation of cylinder **410** causes the nuts **416***a*, **416***b* to move in opposite directions along the rail **418** (e.g., toward

each other). Translation of the nuts in opposite directions applies tension to the first pull wire and introduces slack to the second pull wire, causing the balloon catheter shaft **312** to bend or deflect in a first direction. Rotating the knobs counterclockwise produces rotation of the cylinder **410** in a direction opposite its initial rotation mentioned above. Rotation of cylinder **410** causes the nuts **416***a*, **416***b* to move in opposite directions along the rail **418** (e.g., away each other). Translation of the nuts in opposite directions applies tension to the second pull wire and introduces slack to the first pull wire, causing the balloon catheter shaft **312** to bend or deflect in a second direction, opposite the first direction.

The handle **400** can optionally include a pusher actuation mechanism **422** that is configured to move a pusher device adjacent the distal end of the balloon catheter. The pusher device extends partially over the balloon and holds the prosthetic valve in place on the balloon as the prosthetic valve and balloon catheter are inserted through the introducer. A pusher device is disclosed in co-pending application Ser. No. 12/385,555, which is incorporated herein by reference. The actuation mechanism **422** is pivotably connected to a linkage arm **424**, which in turn is pivotably connected to a proximal holder **426** of the pusher device (not shown). The pusher device can extend from the proximal holder **426** to the balloon **314**. Moving the actuation mechanism **422** to a distal position moves the pusher device in a position partially extending over the balloon **314** and holding the prosthetic valve in place on the balloon for insertion through the introducer **304**. Moving the actuation mechanism **422** to a proximal position moves the pusher device proximally away from the balloon and the prosthetic valve once inside the heart so that the balloon can be inflated for deployment of the prosthetic valve. If a movable pusher device is not used (as in the illustrated balloon catheter **302**), then the pusher actuation mechanism **422** would not be needed. For example, in lieu of or in addition to such a pusher device, stop members **318**, **320** inside the balloon can be used to retain the position of the prosthetic valve on the balloon (FIGS. **33** and **47**A).

FIGS. **43-45** show another embodiment of a handle, indicated at **500**, that can be incorporated in the balloon catheter **302** (in place of handle **308**). The handle **500** comprises a housing **502**, which can be formed from multiple housing sections, including first and second distal housing portions **504**, **506**, respectively, that form a distal housing space, and first and second proximal housing portions **508**, **510**, respectively, that form a proximal housing space. The housing houses a proximal cylinder **512** and a distal cylinder **514**, which house proximal and distal nuts **516**, **518**, respectively. The nuts are disposed on a rail **520** that extends co-axially through the cylinders **512**, **514**. The cylinders **512**, **514** have opposing internal threads, e.g., the proximal cylinder can have right-handed threads and the distal cylinder can have left-handed threads. The cylinders **512**, **514** are secured to each other end-to-end (e.g., with a frictional fit between the distal end of the proximal cylinder and the proximal end of the distal cylinder) so that both rotate together. In other embodiments, the cylinders **512**, **514** can be formed as a single cylinder having left-handed and right-handed threads as used in the handle **400** described above.

A user-engageable, rotatable knob **522** is mounted on the outside of the housing **502** and engages the proximal cylinder **512** (e.g., through an annular gap in the housing) such that rotation of the knob **522** causes corresponding rotation of the cylinders **512**, **514**. The deflection mechanism of this embodiment works in a manner similar to that shown in FIGS. **40-42** to alternatively apply tension and introduce slack in first and second pull wires (not shown) secured to the nuts **516**, **518**, respectively. For example, rotating the knob **522** in a first direction causes the nuts to translate in opposite directions along the rail **520** (e.g., toward each other), which is effective to apply tension to the first pull wire and introduce slack to the second pull wire, causing the balloon catheter shaft **312** to bend or deflect in a first direction. Rotating the knob **522** in a second direction causes the nuts to translate in opposite directions (e.g., away from each other), which is effective to apply tension to the second pull wire and introduce slack to the first pull wire, causing the balloon catheter shaft **312** to bend or deflect in a second direction, opposite the first bending direction.

FIG. **46** discloses a delivery apparatus **600**, according to another embodiment, that can be used to implant an expandable prosthetic heart valve. The delivery apparatus **600** is specifically adapted for use in introducing a prosthetic valve into a heart in a transapical or transaortic procedure. A delivery system for implanting a prosthetic heart valve can comprise the delivery apparatus **600**, an introducer **602** (FIGS. **49-50**), and a loader **604** (FIGS. **51-52**).

Referring to FIGS. **46-47**, the delivery apparatus **600** in the illustrated form is a balloon catheter comprising a handle **606**, a steerable shaft **608** extending from the handle **606**, an inner shaft **610** extending from the handle **606** coaxially through the steerable shaft **608**, an inflatable balloon **612** extending from the distal end of the steerable shaft **608**, a proximal shoulder, or stop member, **614** extending from the distal end of the steerable shaft **608** into the proximal end region of the balloon, a nose cone **616** mounted on the distal end of the inner shaft **610**, and a distal shoulder, or stop member, **618** mounted on the inner shaft **610** within the distal end region of the balloon. The distal stop member **618** can be an integral extension of the nose cone **616** as shown. The proximal stop member **614** can have a proximal end portion **620** secured to the outside surface of the distal end portion of the steerable shaft **608**. The balloon **612** can have a proximal end portion **622** and a distal end portion **624**, with the proximal end portion **622** being secured to the outer surfaces of the shaft **608** and/or the end portion **620** of the proximal stop **614** and the distal end portion **624** being secured to the outer surface of a distal end portion **626** of the distal stop member **618**.

As best shown in FIG. **47**, the proximal end portion **620** of the proximal stop member **614** includes one or more openings **646** for inflation fluid formed in the annular wall between the outer surface of the inner shaft **610** and the inner surface of the outer shaft **608**. The openings **646** allow inflation fluid to flow outwardly from the space between the inner shaft **610** and the outer shaft **608** into the balloon in the distal direction.

The proximal stop member **614** has a distal end portion **628** in form of a substantially cone-shaped member, and the distal stop member **618** has a proximal end portion **630** of the same shape. The spacing between the cone-shaped members **628**, **630** defines an annular space sized to at least partially receive a prosthetic valve that is crimped on the balloon. In use, as shown in FIG. **47**A, the prosthetic valve **12** is crimped onto the balloon between the cone-shaped members **628**, **630** such that the prosthetic valve is retained on the balloon between the cone-shaped members as the prosthetic valve is advanced through the introducer. Desirably, the spacing between the cone-shaped members **628**, **630** is selected such that the prosthetic valve is slightly wedged between the cone-shaped members with the non-inflated balloon extending between the proximal end of the prosthetic valve and the proximal member **628** and between the distal end of the prosthetic valve and the distal member **630**. In addition, the maximum diameter of the members **628**, **630** at their ends adjacent the ends of the prosthetic valve desirably is about the same as or

slightly greater than the outer diameter of the frame of the prosthetic valve **12** when crimped onto the balloon.

As further shown in FIG. **47**, each of the cone-shaped members **628**, **630** desirably is formed with one or more slots **632**. In the illustrated embodiment, each of the cone-shaped members **628**, **630** has three such slots **632** that are equally angularly spaced in the circumferential direction. The slots **632** facilitate radial compression of the cone-shaped members **628**, **630**, which is advantageous during manufacturing of the delivery device and during crimping of the prosthetic valve. In particular, the proximal and distal ends **622**, **624** of the balloon may be relatively smaller than the maximum diameter of the cone-shaped members **628**, **630**. Thus, to facilitate insertion of the cone-shaped members **628**, **630** into the balloon during the assembly process, they can be radially compressed to a smaller diameter for insertion into the balloon and then allowed to expand once inside the balloon. When the prosthetic valve is crimped onto the balloon, the inside surfaces of the crimping device (such as the surfaces of crimping jaws) may contact the cone-shaped members **628**, **630** and therefore will radially compress the cone-shaped members along with the prosthetic valve. Typically, the prosthetic valve will undergo a small amount of recoil (radial expansion) once removed from the crimping device. Due to the compressibility cone-shaped members **628**, **630**, the prosthetic valve can be fully compressed to a crimped state in which the metal frame of the prosthetic valve has an outer diameter equal to or less than the maximum diameter of the cone-shaped members (accounting for recoil of the prosthetic valve).

The slots **632** in the cone-shaped members **628**, **630** also allow inflation fluid to flow radially inwardly through the cone-shaped members and through the region of the balloon extending through the crimped prosthetic valve in order to facilitate expansion of the balloon. Thus, inflation fluid can flow from a proximal region of the balloon, inwardly though slots **632** in proximal stop member **628**, through the region of the balloon extending through the prosthetic valve, outwardly through slots **632** in distal stop **630**, and into a distal region of the balloon. Another advantage of the distal stop member **618** is that it serves a transition region between the nose cone and the prosthetic valve. Thus, when the prosthetic valve is advanced through the leaflets of a native valve, the distal stop member **618** shields the distal end of the prosthetic valve from contacting the surrounding tissue, which can otherwise dislodge or prevent accurate positioning of the prosthetic valve prior to deployment.

The construction of the handle **606** is shown in FIG. **48**. The handle **606** comprises a housing **634**, which can be formed from multiple housing sections. The housing **634** houses a mechanism for effecting controlled articulation/deflection of the shaft **608**. The mechanism in the illustrated embodiment comprises a threaded shaft **636**, and a threaded nut **638** disposed on the shaft. The proximal end portion of the shaft **636** is formed with external threads that engage internal threads of the threaded nut **638**. The shaft **636** can rotate within the handle but is restricted from translational movement within the handle. The nut **638** has opposing flanges **640** (one of which is shown in FIG. **48**), which extend into respective slots formed on the inside surfaces of the housing to prevent rotation of the nut. In this manner, the nut **638** translates along the threads of the shaft **636** upon rotation of the shaft.

The distal end portion of the shaft **636** supports user-engageable, rotatable knob **642**. The shaft **636** is coupled to the knob **12** such that rotation of the knob causes corresponding rotation of the shaft **636**. A pull wire **644** extends from the handle through the balloon catheter shaft **608** on one side of the balloon catheter shaft to its distal end portion. The pull wire **644** has a proximal end secured to the threaded nut **638** inside the handle and a distal end that is secured to the distal end portion of the balloon catheter shaft **608**. The articulation mechanism of this embodiment works by rotating the knob **642** in one direction, which causes the threaded nut **638** to translate along the shaft **636**, which is effective to apply tension to the pull wire causing the balloon catheter shaft **608** to bend or articulate in a predetermined direction. Rotating the knob **642** in the opposite direction causes to the nut **638** to translate in the opposite direction, thereby releasing tension in the pull wire, which allows the shaft **608** to deflect in the opposite direction under its own resiliency. In alternative embodiments, another threaded nut and respective pull wire can be provided in the housing to allow for bi-directional steering of the shaft **608**, as described above in connection with the embodiments of FIGS. **36-45**.

FIG. **49** is a perspective view of the introducer **602**, which comprises an introducer housing assembly **650** and a sheath **652** extending from the housing assembly **650**. The introducer **602** is used to introduce or insert the delivery apparatus **600** into a patient's body. In a transapical procedure, for example, the sheath **652** is inserted through surgical incisions in the chest and the apex of the heart to position the distal end of the sheath in the left ventricle (such as when replacing the native aortic valve). The introducer **602** serves as a port or entry point for inserting the delivery apparatus into the body with minimal blood loss. As shown in FIG. **50**, the introducer housing **650** houses one or more valves **654**, and includes a distal cap **656** to secure sheath **652** to the housing **650** and a proximal cap **658** for mounting the loader **604**.

FIGS. **51-52** are respective and cross-sectional views of the loader **604**, which is used to protect the crimped prosthesis during insertion into the introducer **602**. The loader **604** in the illustrated configuration comprises a distal loader assembly **660** and a proximal loader assembly **662**. The distal loader assembly **660** and proximal loader assembly **662** can be secured to each other by mating female and male threads **680** and **682**, respectively. The distal loader assembly **660** comprises a loader tube **664** and a loader distal cap **666**. The proximal loader assembly **662** comprises a loader housing **668**, a button valve **670**, a washer **672**, two disc valves **674**, and a proximal loader cap **676**. The distal loader cap **666** can be formed with a lip **684** that is configured to engage the proximal cap **658** of the introducer **602** as shown in FIG. **53**.

In use, the proximal loader assembly **662** (apart from the distal loader assembly **660**) can be placed on the balloon catheter shaft **608** prior to placing the prosthetic valve on the balloon and the crimping the prosthetic valve to avoid passing the crimped prosthetic valve through the sealing members **674** inside the housing **668**. After the prosthetic valve is crimped onto the balloon, the distal loader assembly **660** is slid over the crimped prosthetic valve and secured to the proximal loader assembly **662** (by screwing threads **682** into threads **680**). As shown in FIG. **53**, the loader tube **664** (while covering the crimped prosthetic valve) can then be inserted into and through the introducer housing **650** so as to extend through the internal sealing members **654** (FIG. **50**). The loader tube **664** therefore prevents direct contact between the sealing members **654** of the introducer and the crimped prosthetic valve. The loader **604** can be secured to the introducer **602** by pressing the annular lip **684** of the loader into the proximal cap **658** of the introducer. After insertion of the loader tube into the introducer, the prosthetic valve can be advanced from the loader tube, through the sheath **652**, and into a region with the patient's body (e.g., the left ventricle).

As best shown in FIG. **53**, the proximal cap **658** of the introducer comprises first and second diametrically opposed ribbed portions **694** and first and second diametrically opposed, deflectable engaging portions **696** extending between respective ends of the ribbed portions. When the loader **604** is inserted into the introducer **602**, the lip **684** of the loader snaps into place on the distal side of the engaging portions **696**, which hold the loader in place relative to the introducer. In their non-deflected state, the ribbed portions **694** are spaced slightly from the adjacent surfaces of the cap **666** of the loader. To remove the loader from the introducer, the ribbed portions **694** are pressed radially inwardly, which causes the engaging portions **696** to deflect outwardly beyond the lip **684**, allowing the loader and the introducer to be separated from each other.

Fluid (e.g., saline) can be injected into the loader **604** through a lured port **678**, which when pressurized by fluid will allow for fluid flow in a single direction into the loader housing. Alternatively, fluid (e.g., blood, air and/or saline) can be removed from the loader **604** by depressing the crossed portion of the button valve **670**, which creates an opening between the valve **670** and the loader housing. As best shown in FIGS. **52** and **54**, the button **670** in the illustrated embodiment comprises an elastomeric annular ring **686** and a user-engageable projection **688** that extends outwardly through an opening **690** in the loader housing **668**. The ring **686** seals the opening **690** and another opening **692** in the loader housing that communicates with the port **678**. When a pressurized fluid is introduced into the port **678**, the pressure of the fluid causes the adjacent portion of the ring **686** to deflect inwardly and away from its position sealing opening **692**, allowing the fluid to flow into the loader. Alternatively, to remove fluid from the loader, a user can depress projection **688**, which causes the adjacent portion of the ring **686** to deflect inwardly and away from its position sealing the opening **690**, allowing fluid in the loader to flow outwardly through the opening **690**.

General Considerations

For purposes of this description, certain aspects, advantages, and novel features of the embodiments of this disclosure are described herein. The disclosed methods, apparatuses, and systems should not be construed as limiting in any way. Instead, the present disclosure is directed toward all novel and nonobvious features and aspects of the various disclosed embodiments, alone and in various combinations and sub-combinations with one another. The methods, apparatuses, and systems are not limited to any specific aspect or feature or combination thereof, nor do the disclosed embodiments require that any one or more specific advantages be present or problems be solved.

Although the operations of some of the disclosed methods are described in a particular, sequential order for convenient presentation, it should be understood that this manner of description encompasses rearrangement, unless a particular ordering is required by specific language. For example, operations described sequentially may in some cases be rearranged or performed concurrently. Moreover, for the sake of simplicity, the attached figures may not show the various ways in which the disclosed methods can be used in conjunction with other methods. As used herein, the terms "a", "an" and "at least one" encompass one or more of the specified element. That is, if two of a particular element are present, one of these elements is also present and thus "an" element is present. The terms "a plurality of" and "plural" mean two or more of the specified element.

As used herein, the term "and/or" used between the last two of a list of elements means any one or more of the listed elements. For example, the phrase "A, B, and/or C" means "A," "B," "C," "A and B," "A and C," "B and C" or "A, B and C."

As used herein, the term "coupled" generally means physically coupled or linked and does not exclude the presence of intermediate elements between the coupled items absent specific contrary language.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope and spirit of these claims.

We claim:

1. A delivery device for implantation of a prosthetic device within the body, the prosthetic device being radially expandable from a radially compressed state to a radially expanded state, the delivery device comprising:

an inflatable balloon; and

a proximal stop and a distal stop configured to limit longitudinal movement of the prosthetic device relative to the balloon while the prosthetic device is mounted over the balloon in the radially compressed state between the proximal stop and the distal stop;

wherein the proximal stop and the distal stop each comprise an end portion positioned within the balloon and configured to be positioned adjacent a respective end of the prosthetic device when the prosthetic device is radially compressed between the proximal and distal stops, each of the end portions comprising at least one longitudinally extending slot that allows the end portion of the respective stop to be radially compressed to a smaller diameter.

2. The delivery device of claim **1**, wherein the at least one longitudinally extending slot in each stop end portion is configured to allow a balloon-inflation fluid to flow radially through the respective stop.

3. The delivery device of claim **2**, wherein, when the prosthetic device is mounted on the delivery device in the radially compressed state, the proximal stop and the distal stop are configured to allow a balloon-inflation fluid to flow from a proximal portion of the balloon, through the at least one slot in the proximal stop, through an intermediate portion of the balloon positioned within the prosthetic device, through the at least one slot in the distal stop, and into a distal portion of the balloon.

4. The delivery device of claim **1**, wherein a proximal end of the balloon is attached to the proximal stop and a distal end of the balloon is attached to the distal stop.

5. The delivery device of claim **1**, wherein the delivery device further comprises an outer shaft having a lumen and an inner shaft extending through the lumen of the outer shaft, wherein the proximal stop is attached to a distal end of the outer shaft and/or attached to an outer surface of the inner shaft, and wherein the distal stop is attached to an outer surface of the inner shaft.

6. The delivery device of claim **5**, wherein the proximal stop further comprises:

a proximal portion attached to the distal end of the outer shaft and to a proximal end of the balloon; and

an intermediate portion between the proximal portion and the end portion, the intermediate portion having an outer diameter that is less than an outer diameter of the proximal portion and less than the diameter of the end portion.

7. The delivery device of claim 5, wherein the proximal stop is attached to the distal end of the outer shaft and further comprises at least one fluid passageway that allows an inflation fluid to flow through the at least one passageway and into the balloon.

8. The delivery device of claim 5, wherein the distal stop further comprises:

a distal portion attached to a distal end of the balloon; and

an intermediate portion between the distal portion and the end portion, the intermediate portion having an outer diameter that is less than an outer diameter of the distal portion and less than the diameter of the end portion.

9. The delivery device of claim 1, wherein the end portion of each stop decreases in diameter in a direction extending away from the prosthetic device.

10. The delivery device of claim 1, wherein the delivery device further comprises a nosecone attached to a distal end of the distal stop.

11. The delivery device of claim 1, wherein at least one of the stop end portions comprises at least three longitudinal slots that allow the stop end portion to be radially compressed to a smaller diameter when the prosthetic device is crimped onto the delivery device.

12. The delivery device of claim 1, in combination with a prosthetic heart valve crimped onto the balloon between the proximal and distal stops.

* * * * *

US006878168B2

(12) **United States Patent**
Carpentier et al.

(10) **Patent No.: US 6,878,168 B2**
(45) **Date of Patent: Apr. 12, 2005**

(54) **TREATMENT OF BIOPROSTHETIC TISSUES TO MITIGATE POST IMPLANTATION CALCIFICATION**

(75) Inventors: **Sophie M. Carpentier**, Paris (FR); **Alain F. Carpentier**, Paris (FR)

(73) Assignee: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 427 days.

(21) Appl. No.: **10/039,367**

(22) Filed: **Jan. 3, 2002**

(65) **Prior Publication Data**

US 2003/0125813 A1 Jul. 3, 2003

(51) **Int. Cl.**[7] **D01C 3/00**; A61L 27/00
(52) **U.S. Cl.** **8/94.11**; 600/36
(58) **Field of Search** ..... 8/94.11, 94.1 R, 8/94.15, 94.2; 600/36, 2.13, 915, 23.72

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,239,492	A	12/1980	Holman et al.
4,597,762	A	7/1986	Walter et al.
4,713,446	A	12/1987	DeVore et al.
4,798,611	A	1/1989	Freeman, Jr.
4,885,005	A	12/1989	Nashef et al.
4,976,733	A	12/1990	Girardot
5,264,214	A	11/1993	Rhee et al.

FOREIGN PATENT DOCUMENTS

EP	0 065 827	A1	12/1982
EP	0 103 946	A2	3/1984
EP	0 103 947	A2	3/1984
EP	0 347 496	A1	6/1988
EP	0 347 496	B1	6/1988
SU	1651890	A1	5/1991
WO	WO 84/01879	A1	5/1984
WO	WO 89/06945	A1	8/1989
WO	WO 96/04028	A1 *	2/1996

OTHER PUBLICATIONS

Carpentier, Sophie et al., Heat Treatment Mitigates Calcification of Vulvular Bioprostheses, Annals of Thorcic Surgery, vol. 66, No. 6 suppl, Dec. 1998 pp. s264–266.*

"Separation of glutaraldehyde and some of its aidol condensation products by hydroxylaidehyde group affinity chromatography," L. Holmquist, M. Lewin, *Biochem. Bioph Meth*, vol. 22 (1991) pp 321–329.

"The impurities in commercial glutaraldehyde and their effect on the fixation of brain," E. A. Robertson, R. L. Schultz, *J. Ultrastructure Research*, vol. 30 (1970) pp 275–287.

"Weighing the choices in radiation sterilization: Electron–Beam and Gamma," J. Williams, *Medical Device & Diagnostic Industry*, (Mar. 1995) pp 68–72.

"Continuing Improvements in Valvular Bioprostheses," Carpentier, et al. *Journal of Thoracic Cardiovascular Surgery*, (Jan. 1982) pp 27–42.

* cited by examiner

Primary Examiner—Margaret Einsmann
(74) *Attorney, Agent, or Firm*—Rajiv Yaday

(57) **ABSTRACT**

Bioprosthetic tissues are treated by immersing or otherwise contacting fixed, unfixed or partially fixed tissue with a glutaraldehyde solution that has previously been heat-treated or pH adjusted prior to its contact with the tissue. The prior heat treating or pH adjustment of the glutaraldehyde solution causes its free aldehyde concentration to decrease by about 25% or more, preferably by as much as 50%, and allows a "stabilized" glutaraldehyde solution to be obtained at the desired concentration and pH for an optimal fixation of the tissue at high or low temperature. This treatment results in a decrease in the tissue's propensity to calcify after being implanted within the body of a human or animal patient. The heat-treated or pH adjusted glutaraldehyde solution may, in some cases, also be used as a terminal sterilization solution such that the calcification-decreasing treatment with the previously treated glutaraldehyde and a terminal sterilization may be carried out simultaneously and/or in a single container.

28 Claims, 2 Drawing Sheets

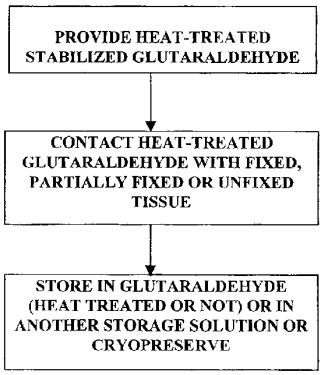


FIGURE 1

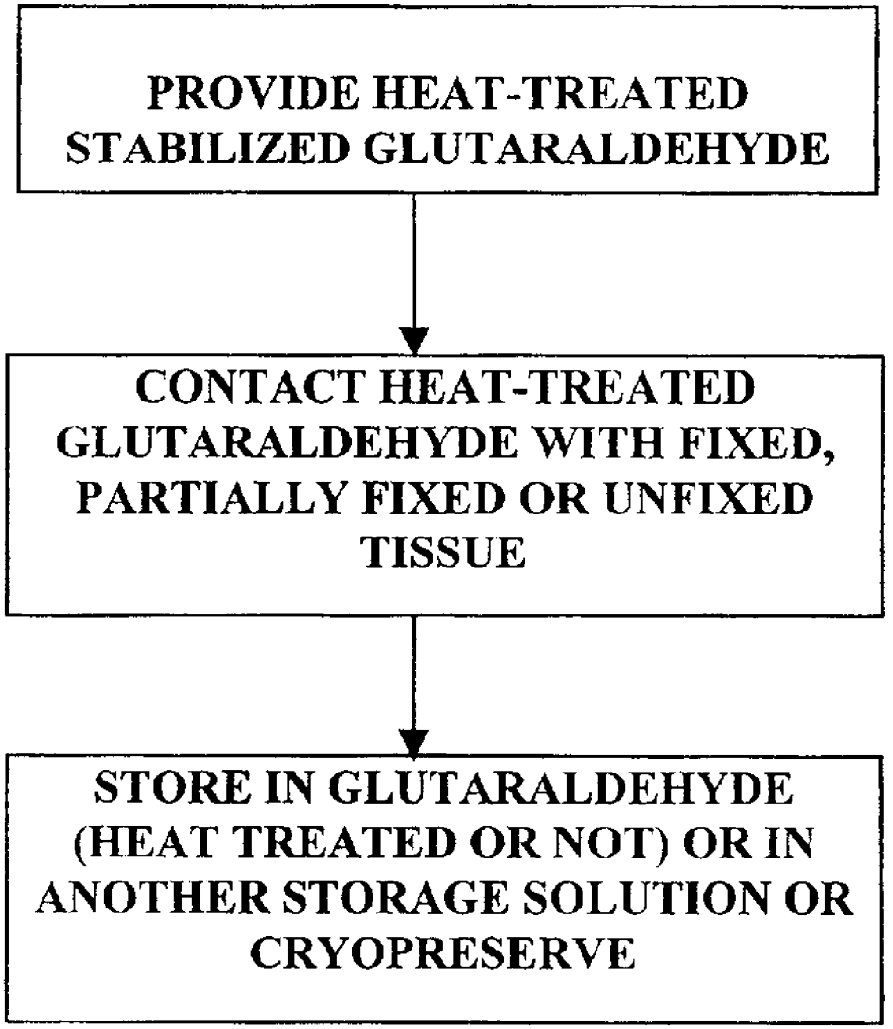
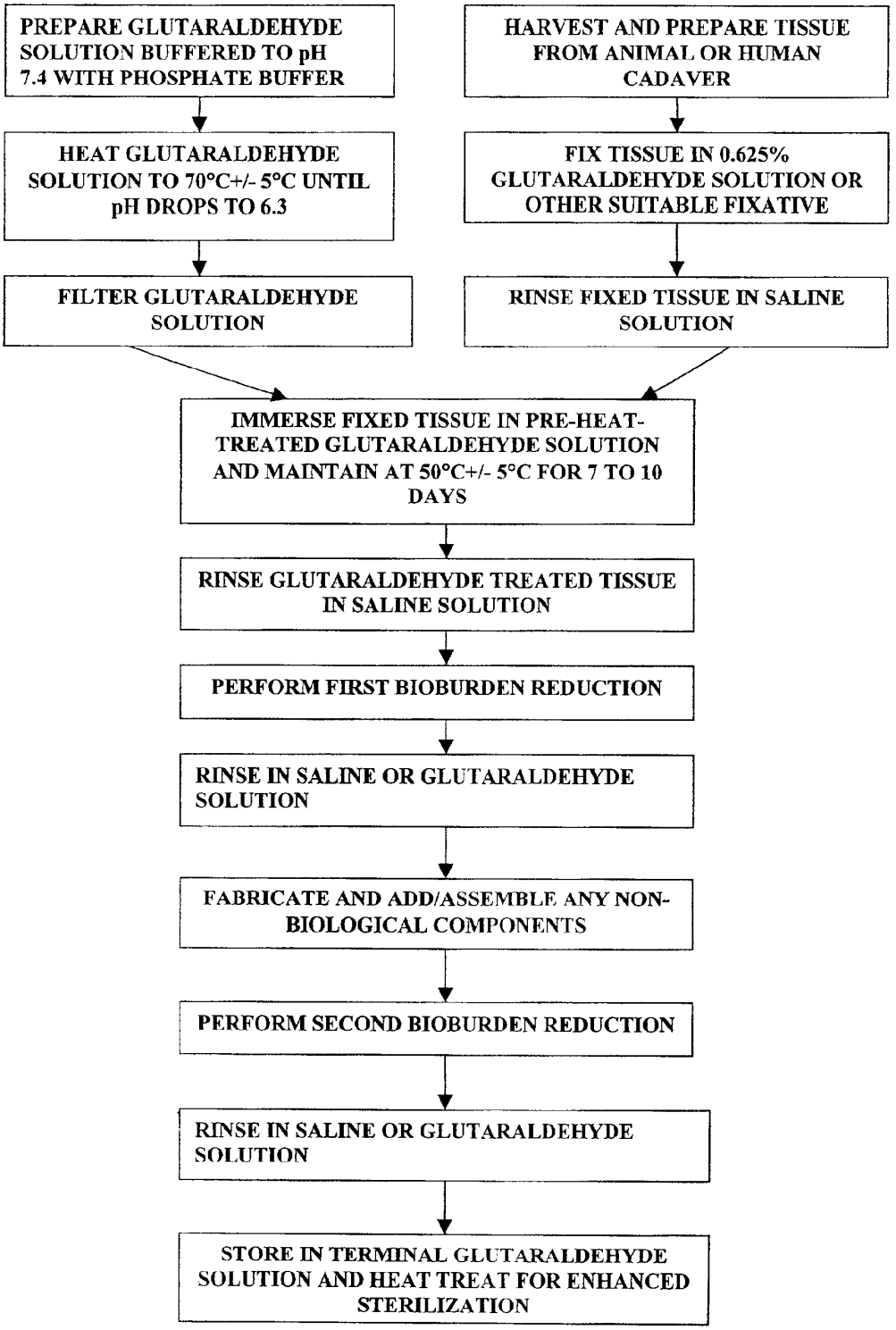

PROVIDE HEAT-TREATED STABILIZED GLUTARALDEHYDE
CONTACT HEAT-TREATED GLUTARALDEHYDE WITH FIXED, PARTIALLY FIXED OR UNFIXED TISSUE
STORE IN GLUTARALDEHYDE (HEAT TREATED OR NOT) OR IN ANOTHER STORAGE SOLUTION OR CRYOPRESERVE

FIGURE 2


PREPARE GLUTARALDEHYDE SOLUTION BUFFERED TO pH 7.4 WITH PHOSPHATE BUFFER
HEAT GLUTARALDEHYDE SOLUTION TO 70°C+/- 5°C UNTIL pH DROPS TO 6.3
FILTER GLUTARALDEHYDE SOLUTION
HARVEST AND PREPARE TISSUE FROM ANIMAL OR HUMAN CADAVER
FIX TISSUE IN 0.625% GLUTARALDEHYDE SOLUTION OR OTHER SUITABLE FIXATIVE
RINSE FIXED TISSUE IN SALINE SOLUTION
IMMERSE FIXED TISSUE IN PRE-HEAT-TREATED GLUTARALDEHYDE SOLUTION AND MAINTAIN AT 50°C+/- 5°C FOR 7 TO 10 DAYS
RINSE GLUTARALDEHYDE TREATED TISSUE IN SALINE SOLUTION
PERFORM FIRST BIOBURDEN REDUCTION
RINSE IN SALINE OR GLUTARALDEHYDE SOLUTION
FABRICATE AND ADD/ASSEMBLE ANY NON-BIOLOGICAL COMPONENTS
PERFORM SECOND BIOBURDEN REDUCTION
RINSE IN SALINE OR GLUTARALDEHYDE SOLUTION
STORE IN TERMINAL GLUTARALDEHYDE SOLUTION AND HEAT TREAT FOR ENHANCED STERILIZATION

TREATMENT OF BIOPROSTHETIC TISSUES TO MITIGATE POST IMPLANTATION CALCIFICATION

FIELD OF THE INVENTION

This invention pertains generally to biomaterials and more particularly to methods for mitigating the post-implantation calcification of bioprosthetic materials and the bioprosthetic devices and articles produced by such methods.

BACKGROUND OF THE INVENTION

Implantable biological tissues can be formed of human tissues preserved by freezing (i.e., cryopreserving) the so called homograft tissues, or of animal tissues preserved by chemically fixing (i.e., tanning) the so called bioprosthesis (Carpentier, Biological Tissues in Heart Valve Replacement, Butterworth (1972), Ionescu editor). The type of biological tissues used as bioprostheses include cardiac valves, blood vessels, skin, dura mater, pericardium, small intestinal submucosa ("SIS tissue"), ligaments and tendons. These biological tissues typically contain connective tissue proteins (i.e., collagen and elastin) that act as the supportive framework of the tissue. The pliability or rigidity of each biological tissue is largely determined by the relative amounts of collagen and elastin present within the tissue and/or by the physical structure and configuration of its connective tissue framework. Collagen is the most abundant connective tissue protein present in most tissues. Each collagen molecule is made up of three (3) polypeptide chains intertwined in a coiled helical configuration.

The techniques used for chemical fixation of biological tissues typically involve the exposure of the biological tissue to one or more chemical fixatives (i.e., tanning agents) that form cross-linkages between the polypeptide chains within a given collagen molecule (i.e., intramolecular crosslinkages), or between adjacent collagen molecules (i.e., intermolecular crosslinkages).

Examples of chemical fixative agents that have been utilized to cross-link collagenous biological tissues include: formaldehyde, glutaraldehyde, dialdehyde starch, hexamethylene diisocyanate and certain polyepoxy compounds. Of the various chemical fixatives available, glutaraldehyde has been the most widely used since the discovery of its anti-immunological and antidegenerative effects by Dr. Carpentier in 1968. See Carpentier, A., J. Thorac. Cardiovascular Surgery, 58: 467–69 (1969). In addition, glutaraldehyde is one of the most efficient sterilization agents. Glutaraldehyde is used as the fixative and the sterilant for many commercially available bioprosthetic products, such as porcine bioprosthetic heart valves (e.g., the Carpentier-Edwards® stented porcine Bioprosthesis), bovine pericardial heart valves (e.g., Carpentier-Edwards® Pericardial Bioprosthesis) and stentless porcine aortic valves (e.g., Edwards PRIMA Plus® Stentless Aortic Bioprosthesis), all manufactured and sold by Edwards Lifesciences LLC, Irvine, Calif.

One problem associated with the implantation of many bioprosthetic materials is that the connective tissue proteins (i.e., collagen and elastin) within these materials can become calcified following implantation within the body. Such calcification can result in undesirable stiffening or degradation of the bioprosthesis. Two (2) types of calcification—intrinsic and extrinsic—are known to occur in fixed collagenous bioprostheses. Intrinsic calcification follows the adsorption

by the tissue of lipoproteins and calcium binding proteins. Extrinsic calcification follows the adhesion of cells (e.g., platelets) to the bioprosthesis and leads to the development of calcium phosphate-containing surface plaques on the bioprosthesis.

The factors that affect the rate at which fixed tissue bioprostheses undergo calcification have not been fully elucidated. However, factors thought to influence the rate of calcification include the patient's age, the existence of metabolic disorders (i.e., hypercalcemia, diabetes, etc.), dietary factors, the presence of infection, parenteral calcium administration, dehydration, in situ distortion of the bioprosthesis (e.g., mechanical stress), inadequate anticoagulation therapy during the initial period following surgical implantation and immunologic host-tissue responses.

Various techniques have heretofore been proposed for mitigating the in situ calcification of glutaraldehyde-fixed bioprostheses or for otherwise improving the glutaraldehyde fixation process. Included among these are the methods described in U.S. Pat. No. 4,729,139 (Nashef) entitled Selective Incorporation of a Polymer into Implantable Biological Tissue to Inhibit Calcification; U.S. Pat. No. 4,885,005 (Nashef et al.) entitled Surfactant Treatment of Implantable Biological Tissue To Inhibit Calcification; U.S. Pat. No. 4,648,881 (Carpentier et al.) entitled Implantable Biological Tissue and Process For Preparation Thereof; U.S. Pat. No. 4,976,733 (Girardot) entitled Prevention of Prosthesis Calcification; U.S. Pat. No. 4,120,649 (Schechter) entitled Transplants; U.S. Pat. No. 5,002,566 (Carpentier) entitled Calcification Mitigation of Bioprosthetic Implants; EP 103947A2 (Pollock et al.) entitled Method For Inhibiting Mineralization of Natural Tissue During Implantation, and U.S. Pat. No. 5,215,541 (Nashef et al.) entitled Surfactant Treatment of Implantable Biological Tissue to Inhibit Calcification. Recently a new technique of calcium mitigation by high temperature fixation of the tissue in glutaraldehyde has been developed and was described in U.S. Pat. No. 5,931,969 (Carpentier et al.) entitled Methods And Apparatus For Treating Biological Tissue To Mitigate Calcification. Although some of these techniques have proven to be efficient in reducing calcification, there remains a need in the art for further improvements of the existing techniques or for the development of new calcification-mitigating techniques to lessen the propensity for post-implantation calcification of fixed bioprosthetic tissues.

SUMMARY OF THE INVENTION

The present invention provides methods for treating tissue to inhibit post implant calcification whereby fixed, unfixed or partially fixed tissue is immersed in or otherwise contacted with a pre-treated glutaraldehyde solution. In a preferred embodiment of the present invention, the glutaraldehyde solution is heat-treated prior to its contact with the tissue. Preferably, the glutaraldehyde solution is heated to a first temperature for a first period of time. The temperature of the glutaraldehyde solution is then adjusted to a second temperature (preferably lower than the first temperature), before contacting the bioprosthetic tissue.

The first temperature to which the glutaraldehyde solution is heated is sufficiently high, and is maintained for sufficiently long, to cause the free aldehyde content and pH of the glutaraldehyde solution to fall by a predetermined amount. Preferably, the prior heat treating of the glutaraldehyde solution causes the free aldehyde concentration of the solution to decrease by about 25%, preferably by about 50%.

The glutaraldehyde solution may be buffered so that the pH is initially in the range of about 7.2 to 7.8, preferably about 7.4. After the heating has been carried out, the pH of the solution will typically have fallen to approximately 5.0 to 7.0, preferably 6.0. Due to the preheating of the glutaraldehyde solution, the solution does not significantly change its chemical characteristics when used to treat the tissue later in the procedure.

In a preferred embodiment, the glutaraldehyde solution is heated to a first temperature of at least 20° C., but preferably not more than 90° C. More preferably, the glutaraldehyde solution is heated to a temperature between about 60° C. to 80° C., and most preferably about 70±5° C. The glutaraldehyde solution may become somewhat yellow in color during this heat-treatment step. The time period during which the first temperature must be maintained will typically vary inversely with the first temperature (i.e., lower temperatures will require a longer period of time to cause a decrease in free aldehyde content and/or a fall in pH). Preferably, the glutaraldehyde is heated to the first temperature for a period of time between about one hour and six months, and more preferably about 1 day to 2 months. Thereafter, the solution is filtered and adjusted to a second temperature before adding the tissue. Preferably, this second temperature may be in the range of about 30 to 70° C., preferably about 40–60° C., and more preferably about 50° C.±5.

In another embodiment of the present invention, glutaraldehyde solution is not heat treated but the pH of the glutaraldehyde solution is adjusted to a pH within the range of about 5.0 to 7.0, and preferably to about 6.0. The pretreated glutaraldehyde solution, whether by preheating or pH adjustment, is then used to treat the tissue, preferably at a temperature in the range of about 30 to 70° C., more preferably at a temperature between about 40 to 60° C., and most preferably, at a temperature of about 50° C.±5° C. In a preferred embodiment, the tissue is treated for a period of time between about one hour to six months, and more preferably for about one day to two months. For example, at a temperature of about 50° C., the preferred period of time is between about 5 days to 10 days, and most preferably, for about seven days.

The heat-treated or pH adjusted glutaraldehyde solution may, in some cases, also be used as a terminal sterilization solution such that the calcification-decreasing treatment with previously treated glutaraldehyde and a terminal sterilization may be carried out simultaneously with the same solution and/or in a single container.

The heat-treated glutaraldehyde solutions may also contain other chemicals to enhance its efficacy, such as surfactants (e.g., Tween 80), alcohol (e.g., ethanol) and/or aldehydes (e.g., formaldehyde).

In another embodiment of the method of the present invention, the tissue is heat treated in a preheated solution other than glutaraldehyde, for example, any other fixative solution or a surfactant solution (e.g., Tween 80 with or without ethanol and/or formaldehyde), or a physiologic solution (e.g., saline or a balanced salt solution). The preheating of the solution is carried out at a temperature between about 20 to 90° C., more preferably between about 37 and 60° C., and most preferably about 45° C., for one hour to six months, preferably one day to two months. In the preheated solution, the tissue is heat treated between about 30 and 70° C., and more preferably about 50° C., for about one day to two months. In another embodiment, the tissue is heat treated in a non-preheat treated physiologic solution wherein the pH has been adjusted between 5.0 and 7.0, preferably 6.0.

The method of the present invention results in a decrease in the tissue's propensity to calcify after being implanted within the body of a human or animal patient. Prior to, concurrently with, or after undergoing treatment with the pre-treated glutaraldehyde, the tissue may be chemically fixed by exposing the tissue to one or more chemical fixatives or cryopreserved by freezing the tissue in accordance with well known techniques.

Further in accordance with the invention, there are provided bioprosthetic devices or articles that are formed, wholly or partially, of tissue that has been treated in accordance with the various embodiments of the method of the present invention. Examples of biological tissues of human or animal origin which may be used in bioprosthetic devices or articles of the present invention include, but are not necessarily limited to: heart valves; venous valves; blood vessels; ureter; tendon; dura mater; skin; pericardium; cartilage (e.g., meniscus); ligament; bone; intestine (e.g., intestinal wall); small intestinal submucosa ("SIS tissue"), and periostium.

Further in accordance with the present invention, there are provided methods for treating diseases and disorders of mammalian patients, by implanting bioprosthetic materials that have undergone the calcification mitigating treatment of the various embodiments of the method of the present invention. Such treatment methods include, but are not limited to, a) the surgical replacement of diseased heart valves with bioprosthetic heart valves that have been treated with glutaraldehyde in accordance with the present invention, b) the repair or bypassing of blood vessels by implanting biological vascular grafts that have been treated with glutaraldehyde in accordance with the present invention, c) the surgical replacement or repair of torn or deficient ligaments by implanting bioprosthetic ligaments that have been treated with glutaraldehyde in accordance with the present invention and, d) the repair, reconstruction, reformation, enhancement, bulking, ingrowth, reconstruction or regeneration of native tissues by implanting one or more biopolymeric or bioprosthetic tissue scaffolds that have been treated with glutaraldehyde in accordance with the present invention (e.g., tissue engineering with a natural tissue or biopolymeric scaffold).

Still further in accordance with this invention, the various embodiments of the method of mitigating post-implantation calcification of bioprosthetic tissues offer significant advantages over previous practices wherein glutaraldehyde was heated in the presence of the tissue, as the present invention allows the desirable features of the heat treatment to be achieved prior to any contact between the glutaraldehyde solution and the tissue, and also allows the temperature of the glutaraldehyde solution to be lowered to about 30 to 70° C., preferably about 40 to 60° C., or most preferably at about 50° C. prior to any contact with the tissue. This lessens the potential for untoward or undesirable reactions to the bioprosthetic tissue due to exposure to high free aldehyde concentrations and/or long term heat treatment at temperatures above 60° C. It also allows for treatment of the tissue within realistic manufacturing time frames.

Still further in accordance with this invention, the method of preheating the solution, and/or heating the tissue, offer better sterilization of both the solution and the tissue at the different stages of the manufacturing process, including the terminal stage. Further aspects and advantages of the present invention will become apparent to those skilled in the relevant art, upon reading and understanding the "Description of Exemplary Embodiments" set forth herebelow.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a flow diagram of one embodiment of the method for mitigating calcification of a bioprosthetic material, in accordance with the present invention.

FIG. **2** is a flow diagram of another embodiment of the method for preparing a bioprosthetic device in accordance with the method of the present invention.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

The following examples are provided for the purpose of describing and illustrating a few exemplary embodiments of the invention only. One skilled in the art will recognize that other embodiments of the invention are possible, but are not described in detail here. Thus, these examples are not intended to limit the scope of the invention in any way.

It has previously been reported that cross-linked bioprosthetic tissue post-treated in 0.625% glutaraldehyde phosphate solution for 2 months at 50° C., with fluid movement (e.g., shaking), exhibited less calcification in the rat subcutaneous and rabbit intramuscular implant models than control cross-linked bioprosthetic tissue fixed in 0.625% glutaraldehyde phosphate solution under typical conditions (i.e., room temperature for 1–14 days). See 66 Ann. Thoracic Surgery 264–6 (1998). Tissues treated under these conditions exhibited a characteristic tan to brown appearance. The heated 0.625% glutaraldehyde phosphate solution also darkened to an amber-brown color and the aldehyde concentration within that solution dropped to about 0.3%.

Since the above publication, the Applicant has discovered that it is advantageous to conduct the heating step on the glutaraldehyde solution prior to its contact with the tissue. The heat-treated glutaraldehyde may then be cooled to a lower temperature and the tissue may then be added to the cooled glutaraldehyde solution under conditions of reduced severity, greater convenience, or both (e.g., shorter time, lower temperature, or both). By heat-treating the glutaraldehyde solution in the absence of the tissue, higher temperatures, concentrations or both can be used during the heat-treating process without risking or causing any adverse effect on the tissue. In another embodiment, the glutaraldehyde solution can be buffered by adjusting the pH of the solution to within a range of about 5.0 to 7.0, preferably about 6.0. Applicants have found that the buffered glutaraldehyde solution has a similar, although slightly less, advantageous effect as the heat-treated glutaraldehyde solution.

The mechanism by which the heat-treated glutaraldehyde mitigates post-implantation calcification is not presently known with certainty. However, Applicants postulate that this calcification mitigating effect is due at least in part to the leaching of lipoproteins and calcium binding proteins and in part to the formation of a calcification mitigating chemical or moiety within the glutaraldehyde solution that acts to limit or inhibit the fixation of calcium into the tissue, either by way of a physical barrier effect (i.e., by retarding diffusion at the boundary layer) and/or by chemically modifying the structure and the surface charge of the tissue and thus its affinity to attract calcium ions. Heat-treated glutaraldehyde can also be used to enhance sterilization by leaving the tissue in the heat-treated glutaraldehyde or by heating the tissue within the previously heat treated glutaraldehyde solution to temperatures between about 37 and 60° C.

A. General Method for Mitigating Calcification of Bioprosthetic Material

FIG. **1** is a flow diagram that generally illustrates one embodiment of the method of the present invention. As shown in FIG. **1**, the first step of the process is to heat treat glutaraldehyde solution in the absence of tissue. It will be appreciated that the concentration of glutaraldehyde in the starting solution may be varied. Thereafter, the solution concentration may be adjusted, if desired, prior to addition of the tissue. It is believed that glutaraldehyde concentrations of as little as 0.1% and as much as 25% or more may be used during the heat-treating step. Reduced glutaraldehyde concentrations of 0.6% to 2.5% have, to date, been successfully obtained and used by Applicant, and those skilled in the art will recognize that higher or lower concentrations of glutaraldehyde may indeed prove to be advantageous during the heat-treating step of the process. The preferred concentration for use during the heat-treating step (FIG. **1**) is 1.0–2.0%. This heat-treating of the glutaraldehyde may be accomplished by heating of the solution until the free aldehyde content of the solution has fallen about 25% or more and remains stable at that level (e.g., a solution of 1.8% falls to about 0.6% or less). Initially, the solution containing glutaraldehyde may be buffered to a pH of 7.4 with a phosphate buffer, a non-phosphate buffer such as a HEPES buffer, or other suitable buffered solutions, and, in such cases, heating of the solution to cause the free aldehyde content to fall will also cause the pH of the solution to fall. In another embodiment of the present invention, rather than heat treating the glutaraldehyde solution, the pH may be adjusted from 7.4 to a pH within the range of about 5.0 to 7.0, preferably 6.0.

The heat-treating of the glutaraldehyde may be accomplished by any suitable means. In this example, the glutaraldehyde is pre-heated to and maintained at a temperature between about 20–90° C., preferably between about 60° C.–80° C., and most preferably 70±5° C. for sufficient period of time to cause the free aldehyde concentration to decrease by at least 25% and to stabilize at a pH of approximately 6.0 (i.e., the pH of 6.0 corresponds to a free aldehyde concentration of about 0.3–0.7%). Depending on the temperature used, the step of heat treating the glutaraldehyde may take anywhere from one hour to six months or more depending on the temperature used. The preferred method is to heat the glutaraldehyde solution to approximately 70±5° C., for approximately 1 day to 2 months or until the desired fall of at least 25% or more in free aldehyde concentration and a pH of approximately 6.0, are observed.

After the heat-treatment of the glutaraldehyde has been completed the solution is cooled to a second temperature that does not cause damage to the tissue (e.g., about 30 to 70° C., preferably about 40 to 60° C., or most preferably at about 50° C.). An unfixed, partially-fixed, or fixed tissue is then contacted with the heat-treated glutaraldehyde. Tissue that has been "fully fixed" in this regard means that the tissue has been fixed to an extent suitable for use as an implant, while "partially fixed" means that the tissue has been fixed to some extent short of being fully fixed. This tissue treatment step is preferably accomplished by immersing fixed, partially fixed or unfixed tissue in the heat-treated glutaraldehyde solution while maintaining the solution at about 30 to 70° C., preferably about 40 to 60° C., or most preferably at about 50° C. It is preferable that the pH of the solution be left at about 6.0 prior to placement of the tissue within the solution. Thereafter, the temperature of the solution is maintained at approximately 50° C. with the tissue immersed in the solution to allow the heat-treated glutaraldehyde solution to interact with or modify the tissue. The tissue's susceptibility to post-implant calcification will be significantly reduced after immersion for as little as one hour to as much as six months or more (depending primarily on the temperature used), but typically occurs within 1 to 15 days at 50° C.

In another embodiment of the method of the present invention, the tissue may be heat treated in a surfactant

solution (e.g., Tween 80 with or without ethanol and/or formaldehyde) or in a physiologic solution (e.g. saline or a balanced salt solution) at a temperature between about 37° C. and 60° C., preferably about 45° C., for about one hour to six months, preferably about one to 15 days, and then heat treated in a glutaraldehyde solution as described above.

Prior to, concurrently with or after the tissue treatment step, the tissue may be cryopreserved or otherwise preserved, i.e. by fixation.

B. An Example of a Method for Manufacturing a Fixed Heterologous Heart Valve Bioprosthesis Having Mitigated Propensity for Post-implantation Calcification

FIG. **2** is a flow diagram of a specific process for manufacturing a bioprosthetic device, such as a stented or stentless porcine heart valve or bovine pericardial heart valve of the type referred to herein. The following is a description of the exemplary process shown in FIG. **2**.

1. Heat-treating of Glutaraldehyde

Prepare Glutaraldehyde Solution

Initially, an aqueous solution of 1.8% by weight glutaraldehyde is prepared in a clean, inert vessel (e.g., a vessel made of stainless steel, plastic or borosilicate glass) and such solution is then buffered to the pH of a approximately 7.4 by adding phosphate buffered saline solution.

Preheat Glutaraldehyde Solution in Absence of Tissue

The glutaraldehyde in the solution is then preheated. Such preheating of the glutaraldehyde is accomplished by heating of the solution to about 70° C.±5° C. and maintaining such temperature until the pH of the solution falls to approximately 6.0. At this point, the color of the solution can be colorless to golden or brown. The fall of the solution pH to 6.0 and the accompanying change in color to golden or brown indicates that the preheating treatment has been completed. This preheating step is typically completed after 1-14 days, preferably 6–8 days, of maintaining the solution at the 70°±5° C. temperature. Higher temperatures ranging up to approximately 90° C. may be used, and the use of such higher temperatures will typically speed the desired fall in free aldehyde concentration and accompanying change in pH (e.g., a solution having a starting pH adjusted to 7.4 will fall to a pH of about 6.0 after approximately 1–3 days at 90° C.). Lower temperatures, ranging downward to approximately 20° C., may also be used, and the use of such lower temperatures will typically cause the desired free aldehyde content and pH changes to take longer. After the heat treatment of the solution has been carried out the solution is filtered.

Optional Neutralization of pH of Heat-treated Glutaraldehyde Solution

After the glutaraldehyde has been heat-treated, the solution is allowed to cool to about 50° C. and its pH may be adjusted at step 24 back to approximately 7.4 by adding phosphate buffered saline or some other suitable buffer.

2. Harvesting, Preparation and Fixation of Tissue:

Harvesting/Preparation of Biological Tissue

The desired biological tissue is harvested from a human cadaver or animal donor, and prepared for subsequent fixation and treatment. The tissue is typically harvested by surgical cutting or removal from its host animal. Thereafter, it is typically trimmed or cut to size and washed with sterile water, basic salt solution, saline or other suitable washing solution.

Fixation of Biological Tissue

The biological tissue may be fixed prior to, during or after its treatment with the heat-treated glutaraldehyde. In this example, the tissue is fixed prior to undergoing the treatment with heat-treated glutaraldehyde. This fixation is carried out by immersing the tissue in a solution of 0.625% by weight glutaraldehyde buffered to a pH of approximately 7.4 by a suitable buffer such as a phosphate buffer, for 1–14 days at ambient temperature. In order to enhance fixation or sterilization other chemical compounds such as surfactants (e.g. Tween 80) and/or ethanol and/or formaldehyde can be added to the glutaraldehyde. It will be appreciated, however, that various other fixatives may be used, such as aldehydes (e.g., formaldehyde, glutaraldehyde, dialdehyde starch) or polyglycidyl ethers (e.g., Denacol 810), or heterologous bifunctional or multifunctional crosslinkers.

Rinsing of Tissue

After it has been removed from the fixative solution, the tissue is thoroughly rinsed with saline solution, basic salt solution or free glutaraldehyde solution or some other suitable washing solution.

3. Treatment of Tissue with Heat-treated Glutaraldehyde to Mitigate Post-implantation Calcification

Immersion of Tissue in Heat-treated Glutaraldehyde Solution

After the fixed tissue has been rinsed, it is treated with the pre-heat treated glutaraldehyde solution. The pre-heat treated glutaraldehyde solution is placed in a vessel such as a stainless steel bath, cooled to and maintained at preferably 50° C.±5° C. The fixed/rinsed tissue is then immersed in the heat-treated glutaraldehyde solution and the solution is continually maintained at 50° C.±5° C. with the tissue immersed in the solution with or without fluid movement. The tissue's susceptibility to post-implant calcification will be significantly reduced after immersion for as little as one hour to as much as six months or more (depending primarily on the temperature used), but typically occurs within 6 to 8 days at 50° C.±5°. Thereafter, the tissue is removed from the solution. The tissue is typically brown in color at this time.

Rinsing of Tissue

After it has been removed from the heat-treated glutaraldehyde solution, the tissue is thoroughly rinsed with saline solution, basic salt solution or some other suitable washing solution.

4. Poststerilization, Assembly/Fabrication and Storage of Bioprosthesis

First Bioburden Reduction (BREP I)

After the tissue has been fixed, treated with the heat-treated glutaraldehyde and rinsed, it is subjected to a first bioburden reduction treatment immersed in or otherwise contacted with a mixture containing i) a crosslinking agent, ii) a denaturing agent and iii) a surfactant (i.e., a CDS solution). One preferred CDS solution (described in U.S. Pat. No. 4,885,005 and U.S. Pat. No. 4,648,881) is a mixture of i) formaldehyde, ii) ethanol and ii) surfactant (e.g., Tween 80™ surfactant, available from ICI Americas, Brantford, Ontario). Such preferred CDS solution may also be referred to by the acronym "FETS" and has a preferred formulation as follows:

Formaldehyde	4.0 ± 0.4% by weight
Ethanol	22.0 ± 2.2% by weight
Tween 80	1.2 ± 0.2% by weight

The tissue is preferably immersed in the CDS solution for 2 hours to 7 days and typically about 2 hours. During this immersion period, the CDS solution is maintained at a temperature of 4–50° C., and preferably at about 20–37° C.

Those skilled in the art will appreciate that various alternative chemical compounds or solutions may be substituted for each component of the CDS solution, as follows:

Potential Alternative Crosslinking Agents

A. Aldehydes: formaldehyde, glutaraldehyde, paraformaldehyde, glyceraldehyde, glyoxal acetaldehyde or acrolein

B. Epoxides: any of the various Denacols and their individual reactive species, including mono, di, tri, and multifunctionalized epoxides

C. Carbodiimides

D. Mixed multifunctional molecules (e.g. aldehyde-epoxide combination)

Potential Alternative Denaturing Agents

A. Alcohols/Solvents: e.g., ethanol, isopropyl alcohol

B. Acidified Ethers: e.g., sulfuric acid/ether mixture, acetone, ethers of small alkyl size (methyl, ethyl, etc. but probably not beyond butyl)

C. Ketones: e.g., methyl ethyl ketone (MEK)

D. Commercial Solvent Systems: e.g., Genesolve™ (Allied Signal, Inc., Morristown, N.J.)

E. Glycols: glycerol ethylene glycol, polyethylene glycol, low molecular weight carbowax

F. Chaotropic Agents: e.g., urea, guanidine hydrochloride, guanidine thiocyanate, potassium iodide

G. High Concentration Salt Solutions: e.g., lithium chloride, sodium chloride, cesium chloride.

Potential Alternative Surfactants

(these surfactant compounds can be used individually or in mixtures such as deoxycholate/Triton or commercially-available mixtures such as Micro-80/90.)

A. Anionic Surfactants: e.g., esters of lauric acid, including but not limited to sodium laurel sulfate (also called sodium dodecyl sulfate)

B. Alkyl sulfonic acid salts: e.g., 1-decanesulfonic acid sodium salt

C. Non-ionic compounds: e.g., compounds based on the polyoxyethylene ether structures, including Triton X-100, 114, 405, N-101 (available commercially from Sigma Chemical, St. Louis, Mo.) and related structures; Pluronic and Tetronic surfactants (available commercially from BASF Chemicals, Mount Olive, N.J.)

D. Alkylated Phenoxypolyethoxy Alcohols: e.g., NP40, Nonidet P40, Igepal, CA630, hydrolyzed/functionalized animal and plant compounds including Tween 80, Tween 20, octyl-derivatives, octyl b-glucoside, octyl b-thioglucopyranoside, deoxycholate and derivatives thereof, zwitterionic compounds, 3-([cholamidopropyl]-dimethyl amino)-1-propanesulfonate (CHAPS), 3-([cholamidopropyl]-dimethyl amino)-2-hydroxy-1-propanesulfonate (CHAPSO) (available from Pierce Biotec Company, Rockford, Ill.).

Fabrication/Assembly

After the first bioburden reduction has been completed, the tissue maybe again rinsed with a suitable rinsing solution such as isotonic saline or 0.625% glutaraldehyde and transported into a clean room or aseptic environment. Thereafter, the tissue may be further trimmed or shaped (if necessary) and attached to or assembled with any non-biological components (e.g., stents, frames, suture rings, conduits, segments of polyester mesh to prevent suture tear-through, etc.) to form the desired bioprosthetic device. Examples of bioprosthetic devices that are assembled of both biological tissue and non-biological components include stented porcine bioprosthetic heart valves (e.g., the Carpentier-Edwards® Bioprosthesis), and bovine pericardial heart valves (e.g., Carpentier-Edwards® Pericardial Bioprosthesis), stentless porcine aortic valves that incorporate fabric reinforcements (e.g., Edwards PRIMA Plus® Stentless Aortic Bioprosthesis), and conduit valves for bio-mechanical ventricular assist devices (e.g., the Novacor N-100PC model), all available from Edwards Lifesciences LLC, Irvine, Calif.

Second Bioburden Reduction (BREP II)

After the bioprosthesis has been fabricated and assembled it is subjected to a second bioburden reduction that is essentially a repeat of the first bioburden reduction described above, however, in this second bioburden reduction step, the solution is preferably maintained at about 37° C. for approximately 2 hours to 10 days, preferably about 9 hours.

Terminal Heating and Storage

After completion of the second bioburden reduction, the tissue (or bioprosthesis) is rinsed with a suitable rinsing solution (such as isotonic saline or 0.625% glutaraldehyde solution) and then placed in a terminal solution for storage and sterilization. The preferred terminal solution is a glutaraldehyde solution having a concentration of about 0.2 to 1.0% by weight glutaraldehyde, and most preferably about 0.625% by weight glutaraldehyde. This solution has a strong sterilizing effect that can be enhanced by a terminal heating of the solution.

In this terminal sterilization step, the tissue (or bioprosthesis) is immersed in or contacted with the terminal solution and heated for a period of time sufficient to ensure sterility of the bioprosthesis until the time of implantation. The period of heating varies depending upon the temperature utilized, i.e., the lower the temperature the longer the period of time. For example, from 1 or 2 hours to 1 month for temperatures between about 50° C. and 20° C., respectively. Preferably, the period of time is 1 to 6 days at 37° C. or 6 hours to 2 days at 50° C., but one of skill in the art will recognize that these temperature or time values can be modified within the scope of the invention.

In order to avoid additional transfer and manipulation, the terminal heating is preferably carried out in the sealed storage container or package in which the bioprosthesis will be shipped and stored until the time of implantation. The tissue (or bioprosthesis) is aseptically deposited in the storage container that has been pre-filled with the 0.625% glutaraldehyde aqueous solution buffered to a pH of 7.4 with sodium hydroxide, such that the tissue (or bioprosthesis) is fully immersed in the buffered glutaraldehyde solution. Thereafter, the container is sealed and placed at room temperature for at least 7 days, or in an oven at 37° C. for 24 hours, or at 50° C. for 6 hours to enhance the sterilization power of glutaraldehyde. Thereafter, the container is cooled to room temperature and shipped to the hospital or other location(s) where it is stored until the time of use of the bioprosthesis.

In another embodiment, the terminal heating is carried out before placing the tissue or bioprosthesis in the storage container.

In some cases, glutaraldehyde that has been heat-treated in accordance with this invention may be used as the terminal solution and, in such cases, it may be possible to shorten or completely eliminate the previous step of immersing the tissue in previously heat-treated glutaraldehyde, opting instead to accomplish some or all of the treatment of the tissue by heat-treated glutaraldehyde until the last step of storage, i.e., concurrently with the terminal sterilization step.

While the foregoing is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Moreover, it will be obvious that certain other modifications may be practiced within the scope of the appended claims.

What is claimed is:

1. A method for mitigating post-implantation calcification of a bioprosthetic material, said method comprising the steps of:

(a) heating a glutaraldehyde solution having a pH of between 7.2–7.8 to a first temperature above 20° C. for a first period of time of at least one hour until the pH of the glutaraldehyde solution has been reduced to between 5–7; and

(c) contacting a quantity of biological tissue that contains connective tissue protein with the pH-reduced glutaraldehyde solution for a second period of time of at least one hour.

2. A method according to claim **1**, wherein the first temperature is maintained for a period of time until the glutaraldehyde solution further exhibits

a decrease of about 25% or more in the free aldehyde content of the solution.

3. A method according to claim **2** wherein the first temperature is no more than about 90° C.

4. A method according to claim **2** wherein the first temperature is about 60–80° C.

5. A method according to claim **2** wherein the first temperature is about 70±5° C.

6. A method according to claim **2** further including the step of:

(b) prior to step (c), adjusting the temperature of the glutaraldehyde solution to a second temperature less than the first temperature.

7. A method according to claim **6** wherein the second temperature is about 30–70° C.

8. A method according to claim **6** wherein the second temperature is about 40–60° C.

9. A method according to claim **6** wherein the second temperature is about 50±5° C.

10. A method according to claim **1** wherein the second temperature is between about 40–60° C.

11. A method according to claim **1** wherein the tissue is fully fixed prior to the performance of Step (c).

12. A method according to claim **11** wherein the tissue is fixed by immersing the tissue in a solution of glutaraldehyde for 1–14 days.

13. A method according to claim **1** wherein the glutaraldehyde solution in Step (c) is moving relative to the tissue.

14. A method according to claim **1** wherein the method comprises:

preparing a solution of 0.1–25% by weight glutaraldehyde;

heating the glutaraldehyde solution to about 20–90° C. in Step (a); and

thereafter immersing the tissue in the glutaraldehyde solution in Step (c) while maintaining the temperature of the solution in the range of about 40° C. to 60° C. for about 1 day to two months.

15. A method according to claim **14** further comprising the step of subjecting the tissue to a bioburden reduction process.

16. A method according to claim **15** wherein the step of subjecting the tissue to a bioburden reduction process comprises contacting the tissue with a bioburden reduction solution containing a surfactant, an aldehyde and an alcohol.

17. A method according to claim **16** wherein the bioburden reduction solution comprises:

Formaldehyde 2–10% by weight;

Ethanol 10–45% by weight; and,

Tween 80 (polyoxyethylene (20) sorbitan monooleate) 0.1–10% by weight.

18. A method according to claim **1**, wherein the first temperature is maintained for a period of time until the pH of the glutaraldehyde solution has been reduced to 6.0.

19. A method according to claim **18**, wherein the pH of the glutaraldehyde solution is initially about 7.4.

20. A method according to claim **1**, wherein the first temperature is maintained for a period of time until the pH of the glutaraldehyde solution has been reduced by about 20%.

21. A method according to claim **20**, wherein the pH of the glutaraldehyde solution is initially about 7.4.

22. A method according to claim **1** wherein the first period of time is one hour to six months.

23. A method according to claim **22** wherein the first period of time is one day to two months.

24. A method according to claim **22** wherein the first period of time is 1–14 days.

25. A method according to claim **22** wherein the first period of time is 6–8 days.

26. A method according to claim **22** wherein the second period of time is shorter than the first period of time.

27. A method according to claim **22** wherein the second period of time is between 1 to 15 days.

28. A method according to claim **27** wherein the second period of time is between 6 to 8 days.

* * * * *

US010053256B2

(12) **United States Patent**
Carpentier et al.

(10) **Patent No.: US 10,053,256 B2**
(45) **Date of Patent: Aug. 21, 2018**

(54) **TREATMENT OF BIOPROSTHETIC TISSUES TO MITIGATE POST IMPLANTATION CALCIFICATION**

(71) Applicant: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(72) Inventors: **Sophie M. Carpentier**, Paris (FR); **Alain F. Carpentier**, Paris (FR)

(73) Assignee: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 175 days.

(21) Appl. No.: **14/158,667**

(22) Filed: **Jan. 17, 2014**

(65) **Prior Publication Data**

US 2014/0130456 A1 May 15, 2014

Related U.S. Application Data

(60) Continuation of application No. 13/352,027, filed on Jan. 17, 2012, now Pat. No. 8,632,608, which is a continuation of application No. 10/992,563, filed on Nov. 18, 2004, now abandoned, which is a division of application No. 10/039,367, filed on Jan. 3, 2002, now Pat. No. 6,878,168.

(51) **Int. Cl.**
A61L 27/36 (2006.01)
B65B 63/08 (2006.01)

(52) **U.S. Cl.**
CPC ***B65B 63/08*** (2013.01); ***A61L 27/3604*** (2013.01); ***A61L 27/3687*** (2013.01); *A61L 2400/02* (2013.01)

(58) **Field of Classification Search**
CPC A61L 27/3683; A61L 27/3687; A61L 27/3691; A61L 27/3604; A61L 2400/02; B65B 63/08
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,931,969	A *	8/1999	Carpentier et al.	8/94.11
6,203,755	B1 *	3/2001	Odland	422/22
2001/0032024	A1 *	10/2001	Cunanan et al.	623/23.72

FOREIGN PATENT DOCUMENTS

WO	96/004028	A1	2/1996

OTHER PUBLICATIONS

S. Carpentier et al., "Annals of Thoracic Surgery", vol. 66, No. 6 Suppl., S264-266 (1998), XP002243892.

* cited by examiner

Primary Examiner — Amina S Khan
(74) *Attorney, Agent, or Firm* — Michelle C. Kim; Darren M. Franklin; Pui Tong Ho

(57) **ABSTRACT**

Bioprosthetic tissues are treated by immersing or otherwise contacting fixed, unfixed or partially fixed tissue with a glutaraldehyde solution that has previously been heat-treated or pH adjusted prior to its contact with the tissue. The prior heat treating or pH adjustment of the glutaraldehyde solution causes its free aldehyde concentration to decrease by about 25% or more, preferably by as much as 50%, and allows a "stabilized" glutaraldehyde solution to be obtained at the desired concentration and pH for an optimal fixation of the tissue at high or low temperature. This treatment results in a decrease in the tissue's propensity to calcify after being implanted within the body of a human or animal patient.

20 Claims, 2 Drawing Sheets

FIGURE 1

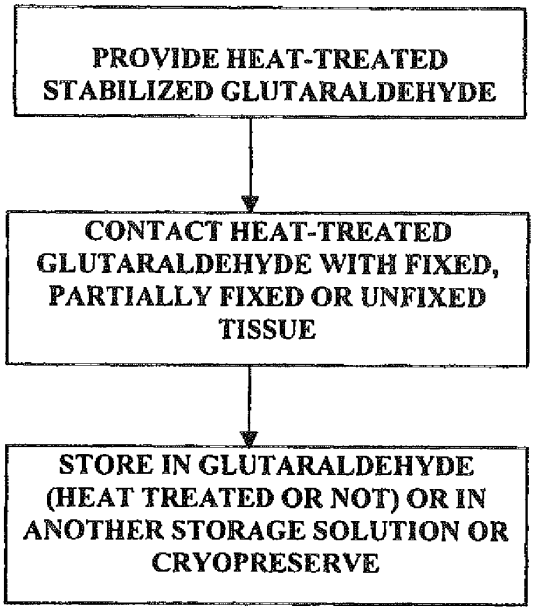
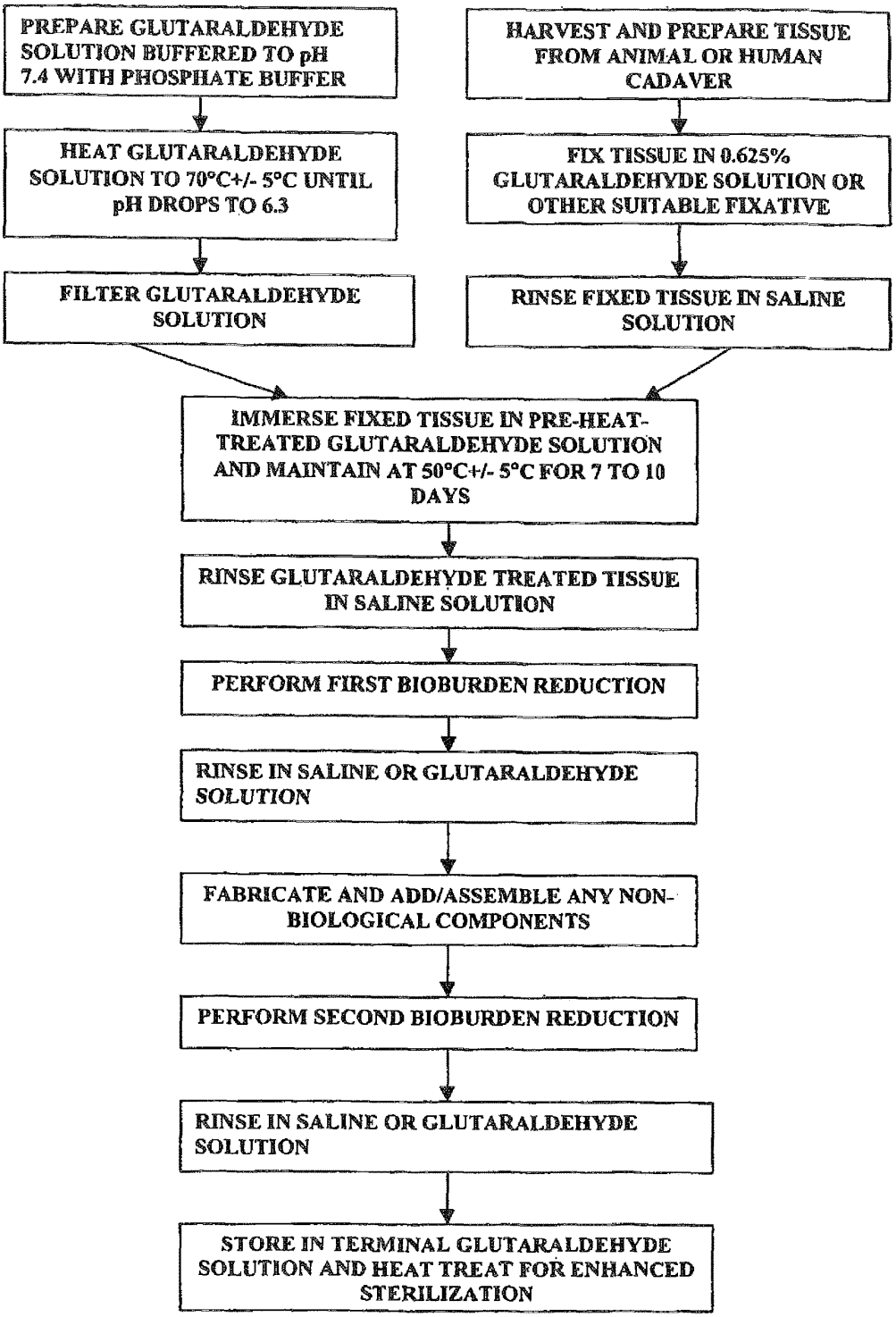

PROVIDE HEAT-TREATED STABILIZED GLUTARALDEHYDE
CONTACT HEAT-TREATED GLUTARALDEHYDE WITH FIXED, PARTIALLY FIXED OR UNFIXED TISSUE
STORE IN GLUTARALDEHYDE (HEAT TREATED OR NOT) OR IN ANOTHER STORAGE SOLUTION OR CRYOPRESERVE

FIGURE 2


PREPARE GLUTARALDEHYDE SOLUTION BUFFERED TO pH 7.4 WITH PHOSPHATE BUFFER
HEAT GLUTARALDEHYDE SOLUTION TO 70°C+/- 5°C UNTIL pH DROPS TO 6.3
FILTER GLUTARALDEHYDE SOLUTION
HARVEST AND PREPARE TISSUE FROM ANIMAL OR HUMAN CADAVER
FIX TISSUE IN 0.625% GLUTARALDEHYDE SOLUTION OR OTHER SUITABLE FIXATIVE
RINSE FIXED TISSUE IN SALINE SOLUTION
IMMERSE FIXED TISSUE IN PRE-HEAT-TREATED GLUTARALDEHYDE SOLUTION AND MAINTAIN AT 50°C+/- 5°C FOR 7 TO 10 DAYS
RINSE GLUTARALDEHYDE TREATED TISSUE IN SALINE SOLUTION
PERFORM FIRST BIOBURDEN REDUCTION
RINSE IN SALINE OR GLUTARALDEHYDE SOLUTION
FABRICATE AND ADD/ASSEMBLE ANY NON-BIOLOGICAL COMPONENTS
PERFORM SECOND BIOBURDEN REDUCTION
RINSE IN SALINE OR GLUTARALDEHYDE SOLUTION
STORE IN TERMINAL GLUTARALDEHYDE SOLUTION AND HEAT TREAT FOR ENHANCED STERILIZATION

TREATMENT OF BIOPROSTHETIC TISSUES TO MITIGATE POST IMPLANTATION CALCIFICATION

RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 13/352,027, filed Jan. 17, 2012 now U.S. Pat. No. 8,632,608, which is a continuation of U.S. patent application Ser. No. 10/992,563, filed Nov. 18, 2004, now abandoned, which is a divisional of U.S. patent application Ser. No. 10/039,367, filed Jan. 3, 2002, now U.S. Pat. No. 6,878,168, all of which are expressly incorporated herein by reference.

FIELD OF THE INVENTION

This invention pertains generally to biomaterials and more particularly to methods for mitigating the post-implantation calcification of bioprosthetic materials and the bioprosthetic devices and articles produced by such methods.

BACKGROUND OF THE INVENTION

Implantable biological tissues can be formed of human tissues preserved by freezing (i.e., cryopreserving) the so called homograft tissues, or of animal tissues preserved by chemically fixing (i.e., tanning) the so called bioprosthesis (Carpentier, Biological Tissues in Heart Valve Replacement, Butterworth (1972), Ionescu editor). The type of biological tissues used as bioprostheses include cardiac valves, blood vessels, skin, dura mater, pericardium, small intestinal submucosa ("SIS tissue"), ligaments and tendons. These biological tissues typically contain connective tissue proteins (i.e., collagen and elastin) that act as the supportive framework of the tissue. The pliability or rigidity of each biological tissue is largely determined by the relative amounts of collagen and elastin present within the tissue and/or by the physical structure and configuration of its connective tissue framework. Collagen is the most abundant connective tissue protein present in most tissues. Each collagen molecule is made up of three (3) polypeptide chains intertwined in a coiled helical configuration.

The techniques used for chemical fixation of biological tissues typically involve the exposure of the biological tissue to one or more chemical fixatives (i.e., tanning agents) that form cross-linkages between the polypeptide chains within a given collagen molecule (i.e., intramolecular crosslinkages), or between adjacent collagen molecules (i.e., intermolecular crosslinkages).

Examples of chemical fixative agents that have been utilized to crosslink collagenous biological tissues include: formaldehyde, glutaraldehyde, dialdehyde starch, hexamethylene diisocyanate and certain polyepoxy compounds. Of the various chemical fixatives available, glutaraldehyde has been the most widely used since the discovery of its antiimmunological and antidegenerative effects by Dr. Carpentier in 1968. See Carpentier, A., J. Thorac. Cardiovascular Surgery, 58: 467-69 (1969). In addition, glutaraldehyde is one of the most efficient sterilization agents. Glutaraldehyde is used as the fixative and the sterilant for many commercially available bioprosthetic products, such as porcine bioprosthetic heart valves (e.g., the Carpentier-Edwards® stented porcine Bioprosthesis), bovine pericardial heart valves (e.g., Carpentier-Edwards® Pericardial Bioprosthesis) and stentless porcine aortic valves (e.g., Edwards PRIMA Plus® Stentless Aortic Bioprosthesis), all manufactured and sold by Edwards Lifesciences LLC, Irvine, Calif.

One problem associated with the implantation of many bioprosthetic materials is that the connective tissue proteins (i.e., collagen and elastin) within these materials can become calcified following implantation within the body. Such calcification can result in undesirable stiffening or degradation of the bioprosthesis. Two (2) types of calcification—intrinsic and extrinsic—are known to occur in fixed collagenous bioprostheses. Intrinsic calcification follows the adsorption by the tissue of lipoproteins and calcium binding proteins. Extrinsic calcification follows the adhesion of cells (e.g., platelets) to the bioprosthesis and leads to the development of calcium phosphate containing surface plaques on the bioprosthesis.

The factors that affect the rate at which fixed tissue bioprostheses undergo calcification have not been fully elucidated. However, factors thought to influence the rate of calcification include the patient's age, the existence of metabolic 'disorders (i.e., hypercalcemia, diabetes, etc.), dietary factors, the presence of infection, parenteral calcium administration, dehydration, in situ distortion of the bioprosthesis (e.g., mechanical stress), inadequate anticoagulation therapy during the initial period following surgical implantation and immunologic host-tissue responses.

Various techniques have heretofore been proposed for mitigating the in situ calcification of glutaraldehyde-fixed bioprostheses or for otherwise improving the glutaraldehyde fixation process. Included among these are the methods described in U.S. Pat. No. 4,729,139 (Nashef) entitled Selective Incorporation of a Polymer into Implantable Biological Tissue to Inhibit Calcification; U.S. Pat. No. 4,885,005 (Nashef et al.) entitled Surfactant Treatment of Implantable Biological Tissue To Inhibit Calcification; U.S. Pat. No. 4,648,881 (Carpentier et al.) entitled Implantable Biological Tissue and Process For Preparation Thereof; U.S. Pat. No. 4,976,733 (Girardot) entitled Prevention of Prosthesis Calcification; U.S. Pat. No. 4,120,649 (Schechter) entitled Transplants; U.S. Pat. No. 5,002,566 (Carpentier) entitled Calcification Mitigation of Bioprosthetic Implants; EP 103947A2 (Pollock et al.) entitled Method For Inhibiting Mineralization of Natural Tissue During Implantation, and U.S. Pat. No. 5,215,541 (Nashef et al.) entitled Surfactant Treatment of Implantable Biological Tissue to Inhibit Calcification. Recently a new technique of calcium mitigation by high temperature fixation of the tissue in glutaraldehyde has been developed and was described in U.S. Pat. No. 5,931,969 (Carpentier et al.) entitled Methods And Apparatus For Treating Biological Tissue To Mitigate Calcification. Although some of these techniques have proven to be efficient in reducing calcification, there remains a need in the art for further improvements of the existing techniques or for the development of new calcification-mitigating techniques to lessen the propensity for post-implantation calcification of fixed bioprosthetic tissues.

SUMMARY OF THE INVENTION

The present invention provides methods for treating tissue to inhibit post implant calcification whereby fixed, unfixed or partially fixed tissue is immersed in or otherwise contacted with a pre-treated glutaraldehyde solution. In a preferred embodiment of the present invention, the glutaraldehyde solution is heat-treated prior to its contact with the tissue. Preferably, the glutaraldehyde solution is heated to a first temperature for a first period of time. The temperature of the glutaraldehyde solution is then adjusted to a second

temperature (preferably lower than the first temperature), before contacting the bioprosthetic tissue.

The first temperature to which the glutaraldehyde solution is heated is sufficiently high, and is maintained for sufficiently long, to cause the free aldehyde content and pH of the glutaraldehyde solution to fall by a predetermined amount. Preferably, the prior heat treating of the glutaraldehyde solution causes the free aldehyde concentration of the solution to decrease by about 25%, preferably by about 50%. The glutaraldehyde solution may be buffered so that the pH is initially in the range of about 7.2 to 7.S, preferably about 7.4. After the heating has been carried out, the pH of the solution will typically have fallen to approximately 5.0 to 7.0, preferably 6.0. Due to the preheating of the glutaraldehyde solution, the solution does not significantly change its chemical characteristics when used to treat the tissue later in the procedure.

In a preferred embodiment, the glutaraldehyde solution is heated to a first temperature of at least 20° C., but preferably not more than 90° C. More preferably, the glutaraldehyde solution is heated to a temperature between about 60° C. to SO° C., and most preferably about 70° C.±5° C. The glutaraldehyde solution may become somewhat yellow in color during this heat-treatment step. The time period during which the first temperature must be maintained will typically vary inversely with the first temperature (Le., lower temperatures will require a longer period of time to cause a decrease in free aldehyde content and/or a fall in pH). Preferably, the glutaraldehyde is heated to the first temperature for a period of time between about one hour and six months, and more preferably about 1 day to 2 months. Thereafter, the solution is filtered and adjusted to a second temperature before adding the tissue. Preferably, this second temperature may be in the range of about 30° C. to 70° C., preferably about 40-60° C., and more preferably about 50° C.±5° C.

In another embodiment of the present invention, glutaraldehyde solution is not heat treated but the pH of the glutaraldehyde solution is adjusted to a pH within the range of about 5.0 to 7.0, and preferably to about 6.0. The pretreated glutaraldehyde solution, whether by preheating or pH adjustment, is then used to treat the tissue, preferably at a temperature in the range of about 30° C. to 70° C., more preferably at a temperature between about 40° C. to 60° C., and most preferably, at a temperature of about 50° C.±5° C. In a preferred embodiment, the tissue is treated for a period of time between about one hour to six months, and more preferably for about one day to two months. For example, at a temperature of about 50° C., the preferred period of time is between about 5 days to 10 days, and most preferably, for about seven days.

The heat-treated or pH adjusted glutaraldehyde solution may, in some cases, also be used as a terminal sterilization solution such that the calcification-decreasing treatment with previously treated glutaraldehyde and a terminal sterilization may be carried out simultaneously with the same solution and/or in a single container.

The heat-treated glutaraldehyde solutions may also contain other chemicals to enhance its efficacy, such as surfactants (e.g., Tween® 80), alcohol (e.g., ethanol) and/or aldehydes (e.g., formaldehyde).

In another embodiment of the method of the present invention, the tissue is heat treated in a preheated solution other than glutaraldehyde, for example, any other fixative solution or a surfactant solution (e.g., Tween® 80 with or without ethanol and/or formaldehyde), or a physiologic solution (e.g., saline or a balanced salt solution). The preheating of the solution is carried out at a temperature between about 20° C. to 90° C., more preferably between about 37° C. and 60° C., and most preferably about 45° C., for one hour to six months, preferably one day to two months. In the preheated solution, the tissue is heat treated between about 30° C. and 70° C., and more preferably about 50° C., for about one day to two months. In another embodiment, the tissue is heat treated in a nonpreheat treated physiologic solution wherein the pH has been adjusted between 5.0 and 7.0, preferably 6.0.

The method of the present invention results in a decrease in the tissue's propensity to calcify after being implanted within the body of a human or animal patient. Prior to, concurrently with, or after undergoing treatment with the pre-treated glutaraldehyde, the tissue may be chemically fixed by exposing the tissue to one or more chemical fixatives or cryopreserved by freezing the tissue in accordance with well known techniques.

Further in accordance with the invention, there are provided bioprosthetic devices or articles that are formed, wholly or partially, of tissue that has been treated in accordance with the various embodiments of the method of the present invention. Examples of biological tissues of human or animal origin which may be used in bioprosthetic devices or articles of the present invention include, but are not necessarily limited to: heart valves; venous valves; blood vessels; ureter; tendon; dura mater; skin; pericardium; cartilage (e.g., meniscus); ligament; bone; intestine (e.g., intestinal wall); small intestinal submucosa ("SIS tissue"), and periostium.

Further in accordance with the present invention, there are provided methods for treating diseases and disorders of mammalian patients, by implanting bioprosthetic materials that have undergone the calcification mitigating treatment of the various embodiments of the method of the present invention. Such treatment methods include, but are not limited to, a) the surgical replacement of diseased heart valves with bioprosthetic heart valves that have been treated with glutaraldehyde in accordance with the present invention, b) the repair or bypassing of blood vessels by implanting biological vascular grafts that have been treated with glutaraldehyde in accordance with the present invention, c) the surgical replacement or repair of torn or deficient ligaments by implanting bioprosthetic ligaments that have been treated with glutaraldehyde in accordance with the present invention and, d) the repair, reconstruction, reformation, enhancement, bulking, ingrowth, reconstruction or regeneration of native tissues by implanting one or more biopolymeric or bioprosthetic tissue scaffolds that have been treated with glutaraldehyde in accordance with the present invention (e.g., tissue engineering with a natural tissue or biopolymeric scaffold).

Still further in accordance with this invention, the various embodiments of the method of mitigating post-implantation calcification of bioprosthetic tissues offer significant advantages over previous practices wherein glutaraldehyde was heated in the presence of the tissue, as the present invention allows the desirable features of the heat treatment to be achieved prior to any contact between the glutaraldehyde solution and the tissue, and also allows the temperature of the glutaraldehyde solution to be lowered to about 30° C. to 70° C., preferably about 40° C. to 60° C., or most preferably at about 50° C. prior to any contact with the tissue. This lessens the potential for untoward or undesirable reactions to the bioprosthetic tissue due to exposure to high free aldehyde concentrations and/or long term heat treatment at

temperatures above 60° C. It also allows for treatment of the tissue within realistic manufacturing time frames.

Still further in accordance with this invention, the method of preheating the solution, and/or heating the tissue, offer better sterilization of both the solution and the tissue at the different stages of the manufacturing process, including the terminal stage. Further aspects and advantages of the present invention will become apparent to those skilled in the relevant art, upon reading and understanding the "Description of Exemplary Embodiments" set forth herebelow.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a flow diagram of one embodiment of the method for mitigating calcification of a bioprosthetic material, in accordance with the present invention.

FIG. **2** is a flow diagram of another embodiment of the method for preparing a bioprosthetic device in accordance with the method of the present invention.

DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

The following examples are provided for the purpose of describing and illustrating a few exemplary embodiments of the invention only. One skilled in the art will recognize that other embodiments of the invention are possible, but are not described in detail here. Thus, these examples are not intended to limit the scope of the invention in any way.

It has previously been reported that cross-linked bioprosthetic tissue post-treated in 0.625% glutaraldehyde phosphate solution for 2 months at 50° C., with fluid movement (e.g., shaking), exhibited less calcification in the rat subcutaneous and rabbit intramuscular implant models than control cross-linked bioprosthetic tissue fixed in 0.625% glutaraldehyde phosphate solution under typical conditions (Le., room temperature for 1-14 days). See 66 Ann. Thoracic Surgery 264-6 (1998). Tissues treated under these conditions exhibited a characteristic tan to brown appearance. The heated 0.625% glutaraldehyde phosphate solution also darkened to an amber-brown color and the aldehyde concentration within that solution dropped to about 0.3%.

Since the above publication, the Applicant has discovered that it is advantageous to conduct the heating step on the glutaraldehyde solution prior to its contact with the tissue. The heat-treated glutaraldehyde may then be cooled to a lower temperature and the tissue may then be added to the cooled glutaraldehyde solution under conditions of reduced severity, greater convenience, or both (e.g., shorter time, lower temperature, or both). By heat-treating the glutaraldehyde solution in the absence of the tissue, higher temperatures, concentrations or both can be used during the heat-treating process without risking or causing any adverse effect on the tissue. In another embodiment, the glutaraldehyde solution can be buffered by adjusting the pH of the solution to within a range of about 5.0 to 7.0, preferably about 6.0. Applicants have found that the buffered glutaraldehyde solution has a similar, although slightly less, advantageous effect as the heat-treated glutaraldehyde solution.

The mechanism by which the heat-treated glutaraldehyde mitigates post-implantation calcification is not presently known with certainty. However, Applicants postulate that this calcification mitigating effect is due at least in part to the leaching of lipoproteins and calcium binding proteins and in part to the formation of a calcification mitigating chemical or moiety within the glutaraldehyde solution that acts to limit or inhibit the fixation of calcium into the tissue, either by way of a physical barrier effect (i.e., by retarding diffusion at the boundary layer) and/or by chemically modifying the structure and the surface charge of the tissue and thus its affinity to attract calcium ions. Heat-treated glutaraldehyde can also be used to enhance sterilization by leaving the tissue in the heat-treated glutaraldehyde or by heating the tissue within the previously heat treated glutaraldehyde solution to temperatures between about 37° C. and 60° C.

A. General Method for Mitigating Calcification of Bioprosthetic Material

FIG. **1** is a flow diagram that generally illustrates one embodiment of the method of the present invention. As shown in FIG. **1**, the first step of the process is to heat treat glutaraldehyde solution in the absence of tissue. It will be appreciated that the concentration of glutaraldehyde in the starting solution may be varied. Thereafter, the solution concentration may be adjusted, if desired, prior to addition of the tissue. It is believed that glutaraldehyde concentrations of as little as 0.1% and as much as 25% or more may be used during the heat-treating step. Reduced glutaraldehyde concentrations of 0.6% to 2.5% have, to date, been successfully obtained and used by Applicant, and those skilled in the art will recognize that higher or lower concentrations of glutaraldehyde may indeed prove to be advantageous during the heat-treating step of the process. The preferred concentration for use during the heat-treating step (FIG. **1**) is 1.0-2.0%. This heat-treating of the glutaraldehyde may be accomplished by heating of the solution until the free aldehyde content of the solution has fallen about 2S% or more and remains stable at that level (e.g., a solution of 1.8% falls to about 0.6% or less). Initially, the solution containing glutaraldehyde may be buffered to a pH of 7.4 with a phosphate buffer, a non-phosphate buffer such as a HEPES buffer, or other suitable buffered solutions, and, in such cases, heating of the solution to cause the free aldehyde content to fall will also cause the pH of the solution to fall. In another embodiment of the present invention, rather than heat treating the glutaraldehyde solution, the pH may be adjusted from 7.4 to a pH within the range of about 5.0 to 7.0, preferably 6.0.

The heat-treating of the glutaraldehyde may be accomplished by any suitable means. In this example, the glutaraldehyde is pre-heated to and maintained at a temperature between about 20-90° C., preferably between about 60° C.-80° C., and most preferably 70° C.±5° C. for a sufficient period of time to cause the free aldehyde concentration to decrease by at least 2S% and to stabilize at a pH of approximately 6.0 (i.e., the pH of 6.0 corresponds to a free aldehyde concentration of about 0.3-0.7%). Depending on the temperature used, the step of heat treating the glutaraldehyde may take anywhere from one hour to six months or more depending on the temperature used. The preferred method is to heat the glutaraldehyde solution to approximately 70° C.±5° C., for approximately 1 day to 2 months or until the desired fall of at least 2S% or more in free aldehyde concentration and a pH of approximately 6.0, are observed.

After the heat-treatment of the glutaraldehyde has been completed the solution is cooled to a second temperature that does not cause damage to the tissue (e.g., about 30° C. to 70° C., preferably about 40° C. to 60° C., or most preferably at about SO° C.). An unfixed, partially-fixed, or fixed tissue is then contacted with the heat-treated glutaraldehyde. Tissue that has been "fully fixed" in this regard means that the tissue has been fixed to an extent suitable for use as an implant, while "partially fixed" means that the tissue has been fixed to some extent short of being fully

fixed. This tissue treatment step is preferably accomplished by immersing fixed, partially fixed or unfixed tissue in the heat-treated glutaraldehyde solution while maintaining the solution at about 30° C. to 70° C., preferably about 40° C. to 60° C., or most preferably at about 50° C. It is preferable that the pH of the solution be left at about 6.0 prior to placement of the tissue within the solution. Thereafter, the temperature of the solution is maintained at approximately 50° C. with the tissue immersed in the solution to allow the heat-treated glutaraldehyde solution to interact with or modify the tissue. The tissue's susceptibility to post-implant calcification will be significantly reduced after immersion for as little as one hour to as much as six months or more (depending primarily on the temperature used), but typically occurs within 1 to 15 days at 50° C.

In another embodiment of the method of the present invention, the tissue may be heat treated in a surfactant solution (e.g., Tween® 80 with or without ethanol and/or formaldehyde) or in a physiologic solution (e.g. saline or a balanced salt solution) at a temperature between about 37° C. and 60° C., preferably about 45° C., for about one hour to six months, preferably about one to 15 days, and then heat treated in a glutaraldehyde solution as described above.

Prior to, concurrently with or after the tissue treatment step, the tissue may be cryopreserved or otherwise preserved, i.e. by fixation.

B. An Example of a Method for Manufacturing a Fixed Heterologous Heart Valve Bioprosthesis Having Mitigated Propensity for Post-Implantation Calcification

FIG. **2** is a flow diagram of a specific process for manufacturing a bioprosthetic device, such as a stented or stentless porcine heart valve or bovine pericardial heart valve of the type referred to herein. The following is a description of the exemplary process shown in FIG. **2**.

1. Heat-Treating of Glutaraldehyde

Prepare Glutaraldehyde Solution

Initially, an aqueous solution of 1.8% by weight glutaraldehyde is prepared in a clean, inert vessel (e.g., a vessel made of stainless steel, plastic or borosilicate glass) and such solution is then buffered to the pH of approximately 7.4 by adding phosphate buffered saline solution.

Preheat Glutaraldehyde Solution in Absence of Tissue

The glutaraldehyde in the solution is then preheated. Such preheating of the glutaraldehyde is accomplished by heating of the solution to about 70° C.±SoC and maintaining such temperature until the pH of the solution falls to approximately 6.0. At this point, the color of the solution can be colorless to golden or brown. The fall of the solution pH to 6.0 and the accompanying change in color to golden or brown indicates that the preheating treatment has been completed. This preheating step is typically completed after 1-14 days, preferably 6-8 days, of maintaining the solution at the 70° C.±5° C. temperature. Higher temperatures ranging up to approximately 90° C. may be used, and the use of such higher temperatures will typically speed the desired fall in free aldehyde concentration and accompanying change in pH (e.g., a solution having a starting pH adjusted to 7.4 will fall to a pH of about 6.0 after approximately 1-3 days at 90° C.). Lower temperatures, ranging downward to approximately 20° C., may also be used, and the use of such lower temperatures will typically cause the desired free aldehyde content and pH changes to take longer. After the heat treatment of the solution has been carried out the solution is filtered.

Optional Neutralization of pH of Heat-Treated Glutaraldehyde Solution

After the glutaraldehyde has been heat-treated, the solution is allowed to cool to about SO° C. and its pH may be adjusted at step 24 back to approximately 7.4 by adding phosphate buffered saline or some other suitable buffer.

2. Harvesting, Preparation and Fixation of Tissue:

Harvesting/Preparation of Biological Tissue

The desired biological tissue is harvested from a human cadaver or animal donor, and prepared for subsequent fixation and treatment. The tissue is typically harvested by surgical cutting or removal from its host animal. Thereafter, it is typically trimmed or cut to size and washed with sterile water, basic salt solution, saline or other suitable washing solution.

Fixation of Biological Tissue

The biological tissue may be fixed prior to, during or after its treatment with the heat-treated glutaraldehyde. In this example, the tissue is fixed prior to undergoing the treatment with heat-treated glutaraldehyde. This fixation is carried out by immersing the tissue in a solution of 0.625% by weight glutaraldehyde buffered to a pH of approximately 7.4 by a suitable buffer such as a phosphate buffer, for 1-14 days at ambient temperature. In order to enhance fixation or sterilization other chemical compounds such as surfactants (e.g. Tween® 80) and/or ethanol and/or formaldehyde can be added to the glutaraldehyde. It will be appreciated, however, that various other fixatives may be used, such as aldehydes (e.g., formaldehyde, glutaraldehyde, dialdehyde starch) or polyglycidyl ethers (e.g., Denacol 810), or heterologous bifunctional or multifunctional crosslinkers.

Rinsing of Tissue

After it has been removed from the fixative solution, the tissue is thoroughly rinsed with saline solution, basic salt solution or free glutaraldehyde solution or some other suitable washing solution.

3. Treatment of Tissue with Heat-Treated Glutaraldehyde to Mitigate Post-Implantation Calcification:

Immersion of Tissue in Heat-Treated Glutaraldehyde Solution

After the fixed tissue has been rinsed, it is treated with the pre-heat treated glutaraldehyde solution. The pre-heat treated glutaraldehyde solution is placed in a vessel such as a stainless steel bath, cooled to and maintained at preferably 50° C.±5° C. The fixed/rinsed tissue is then immersed in the heat-treated glutaraldehyde solution and the solution is continually maintained at 50° C.±5° C. with the tissue immersed in the solution with or without fluid movement. The tissue's susceptibility to post-implant calcification will be significantly reduced after immersion for as little as one hour to as much as six months or more (depending primarily on the temperature used), but typically occurs within 6 to 8 days at 50° C.±5° . Thereafter, the tissue is removed from the solution. The tissue is typically brown in color at this time.

Rinsing of Tissue

After it has been removed from the heat-treated glutaraldehyde solution, the tissue is thoroughly rinsed with saline solution, basic salt solution or some other suitable washing solution.

4. Poststerilization, Assembly/Fabrication and Storage of Bioprosthesis

First Bioburden Reduction (BREP I)

After the tissue has been fixed, treated with the heat-treated glutaraldehyde and rinsed, it is subjected to a first bioburden reduction treatment immersed in or otherwise contacted with a mixture containing i) a crosslinking agent, ii) a denaturing agent and iii) a surfactant (i.e., a CDS solution). One preferred CDS solution (described in U.S. Pat. No. 4,885,005 and U.S. Pat. No. 4,648,881) is a mixture

of i) formaldehyde, ii) ethanol and ii) surfactant (e.g., Tween® 80 surfactant, available from ICI Americas, Brantford, Ontario). Such preferred CDS solution may also be referred to by the acronym "FETS" and has a preferred formulation as follows:

Formaldehyde 4.0.±.0.4% by weight

Ethanol 22.0.±.2.2% by weight

Tween® 80 1.2.±.0.2% by weight

The tissue is preferably immersed in the CDS solution for 2 hours to 7 days and typically about 2 hours. During this immersion period, the CDS solution is maintained at a temperature of 4-50° C., and preferably at about 20-37° C.

Those skilled in the art will appreciate that various alternative chemical compounds or solutions may be substituted for each component of the CDS solution, as follows:

Potential Alternative Crosslinking Agents:

A. Aldehydes: formaldehyde, glutaraldehyde, paraformaldehyde, glyceraldehyde, glyoxal acetaldehyde or acrolein

B. Epoxides: any of the various Denacols and their individual reactive species, including mono, di, tri, and multi-functionalized epoxides

C. Carbodiimides

D. Mixed multifunctional molecules (e.g. aldehyde-epoxide combination)

Potential Alternative Denaturing Agents:

A. Alcohols/Solvents: e.g., ethanol, isopropyl alcohol

B. Acidified Ethers: e.g., sulfuric acid/ether mixture, acetone, ethers of small alkyl size (methyl, ethyl, etc. but probably not beyond butyl)

C. Ketones: e.g., methyl ethyl ketone (MEK)

D. Commercial Solvent Systems: e.g., Genesolve™ (Allied Signal, Inc., Morristown, N.J.)

E. Glycols: glycerol ethylene glycol, polyethylene glycol, low molecular weight carbowax

F. Chaotropic Agents: e.g., urea, guanidine hydrochloride, guanidine thiocyanate, potassium iodide

G. High Concentration Salt Solutions: e.g., lithium chloride, sodium chloride, cesium chloride.

Potential Alternative Surfactants:

(these surfactant compounds can be used individually or in mixtures such as deoxycholate/Triton or commercially-available mixtures such as Micro-80/90.)

A. Anionic Surfactants: e.g., esters of lauric acid, including but not limited to sodium laurel sulfate (also called sodium dodecyl sulfate)

B. Alkyl sulfonic acid salts: e.g., 1-decanesulfonic acid sodium salt

C. Non-ionic compounds: e.g., compounds based on the polyoxyethylene ether structures, including Triton X-IOO, 114, 405, N-101 (available commercially from Sigma Chemical, St. Louis, Mo.) and related structures; Pluronic and Tetronic surfactants (available commercially from BASF Chemicals, Mount Olive, N.J.)

D. Alkylated Phenoxypolyethoxy Alcohols: e.g., NP40, Nonidet P40, Igepal, CA630, hydrolyzedlfunctionalized animal and plant compounds including Tween® 80, Tween® 20, octyl-derivatives, octyl b-glucoside, octyl bthioglucopyranoside, deoxycholate and derivatives thereof, zwitterionic compounds, 3-([cholamidopropyl]-dimethyl amino)-1-propanesulfonate (CHAPS), 3-([cholamidopropyl]-dimethyl amino)-2-hydroxy-1-propanesulfonat-e (CHAPSO) (available from Pierce Biotec Company, Rockford, Ill.).

Fabrication/Assembly

After the first bioburden reduction has been completed, the tissue maybe again rinsed with a suitable rinsing solution such as isotonic saline or 0.625% glutaraldehyde and transported into a clean room or aseptic environment. Thereafter, the tissue may be further trimmed or shaped (if necessary) and attached to or assembled with any non-biological components (e.g., stents, frames, suture rings, conduits, segments of polyester mesh to prevent suture tear-through, etc.) to form the desired bioprosthetic device. Examples of bioprosthetic devices that are assembled of both biological tissue and non-biological components include stented porcine bioprosthetic heart valves (e.g., the Carpentier-Edwards® Bioprosthesis), and bovine pericardial heart valves (e.g., Carpentier-Edwards® Pericardial Bioprosthesis), stentless porcine aortic valves that incorporate fabric reinforcements (e.g., Edwards PRIMA Plus® Stentless Aortic Bioprosthesis), and conduit valves for bio-mechanical ventricular assist devices (e.g., the Novacor N-100PC model), all available from Edwards Lifesciences LLC, Irvine, Calif.

Second Bioburden Reduction (BREP II)

After the bioprosthesis has been fabricated and assembled it is subjected to a second bioburden reduction that is essentially a repeat of the first bioburden reduction described above, however, in this second bioburden reduction step, the solution is preferably maintained at about 37° C. for approximately 2 hours to 10 days, preferably about 9 hours.

Terminal Heating and Storage

After completion of the second bioburden reduction, the tissue (or bioprosthesis) is rinsed with a suitable rinsing solution (such as isotonic saline or 0.625% glutaraldehyde solution) and then" placed in a terminal solution for storage and sterilization. The preferred terminal solution is a glutaraldehyde solution having a concentration of about 0.2 to 1.0% by weight glutaraldehyde, and most preferably about 0.625% by weight glutaraldehyde. This solution has a strong sterilizing effect that can be enhanced by a terminal heating of the solution.

In this terminal sterilization step, the tissue (or bioprosthesis) is immersed in or contacted with the terminal solution and heated for a period of time sufficient to ensure sterility of the bioprosthesis until the time of implantation. The period of heating varies depending upon the temperature utilized, i.e., the lower the temperature the longer the period of time. For example, from 1 or 2 hours to 1 month for temperatures between about 50° C. and 20° C., respectively. Preferably, the period of time is 1 to 6 days at 37° C. or 6 hours to 2 days at 50° C., but one of skill in the art will recognize that these temperature or time values can be modified within the scope of the invention.

In order to avoid additional transfer and manipulation, the terminal heating is preferably carried out in the sealed storage container or package in which the bioprosthesis will be shipped and stored until the time of implantation. The tissue (or bioprosthesis) is aseptically deposited in the storage container that has been pre-filled with the 0.625% glutaraldehyde aqueous solution buffered to a pH of 7.4 with sodium hydroxide, such that the tissue (or bioprosthesis) is fully immersed in the buffered glutaraldehyde solution. Thereafter, the container is sealed and placed at room temperature for at least 7 days, or in an oven at 37° C. for 24 hours, or at 50° C. for 6 hours to enhance the sterilization power of glutaraldehyde. Thereafter, the container is cooled to room temperature and shipped to the hospital or other location(s) where it is stored until the time of use of the bioprosthesis.

In another embodiment, the terminal heating is carried out before placing the tissue or bioprosthesis in the storage container.

In some cases, glutaraldehyde that has been heat-treated in accordance with this invention may be used as the terminal solution and, in such cases, it may be possible to

shorten or completely eliminate the previous step of immersing the tissue in previously heat-treated glutaraldehyde, opting instead to accomplish some or all of the treatment of the tissue by heat-treated glutaraldehyde until the last step of storage, i.e., concurrently with the terminal sterilization step.

While the foregoing is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Moreover, it will be obvious that certain other modifications may be practiced within the scope of the appended claims.

What is claimed is:

1. A method for mitigating post-implantation calcification of a bioprosthetic implant material comprising:

heating a glutaraldehyde solution to a temperature of about 70° C.+/−5° C. for about 6-8 days;

immersing a biological tissue in the glutaraldehyde solution after the heating;

assembling an implantable bioprosthesis using the biological tissue after the immersing;

packaging the implantable bioprosthesis in a sealed package; and

subjecting the packaged implantable bioprosthesis to a terminal sterilization process.

2. The method of claim **1**, wherein the biological tissue is unfixed prior to being immersed in the glutaraldehyde solution.

3. The method of claim **1**, wherein the biological tissue is fixed or partially-fixed before being immersed in the glutaraldehyde solution.

4. The method of claim **1**, wherein the glutaraldehyde solution is heated until a free aldehyde concentration of the glutaraldehyde solution decreases by at least 25%.

5. The method of claim **1**, wherein the glutaraldehyde solution is heated until a pH of the glutaraldehyde solution is approximately 6.0.

6. The method of claim **1**, further comprising subjecting the biological tissue to a first bioburden reduction treatment.

7. The method of claim **6**, wherein the first bioburden reduction treatment comprises immersing the biological tissue in a mixture comprising one or more of a crosslinking agent, a denaturing agent and a surfactant.

8. The method of claim **6**, wherein the first bioburden reduction treatment comprises immersing the biological tissue in a solution of formaldehyde, ethanol and polyoxyethylene sorbitan monooleate.

9. The method of claim **6**, wherein the first bioburden reduction treatment is performed before the assembling.

10. The method of claim **9**, further comprising subjecting implantable bioprosthesis to a second bioburden reduction treatment before the packaging.

11. The method of claim **10**, wherein the second bioburden reduction treatment comprises immersing the biological tissue with a mixture comprising one or more of a crosslinking agent, a denaturing agent and a surfactant.

12. The method of claim **10**, wherein the second bioburden reduction treatment comprises immersing the biological tissue in a solution of formaldehyde, ethanol and polyoxyethylene sorbitan monooleate.

13. The method of claim **12**, wherein the second bioburden reduction treatment solution is maintained at 37° C. for approximately 2 hours to 10 days.

14. The method of claim **1**, wherein the terminal sterilization process uses a terminal sterilization solution.

15. The method of claim **14**, wherein the terminal sterilization solution is a glutaraldehyde solution having a concentration of about 0.2 to 1.0% by weight glutaraldehyde.

16. The method of claim **14**, wherein the terminal sterilization solution is heated to a temperature of between 20° to 50° C. for 1 or 2 hours to 1 month.

17. The method of claim **14**, wherein the terminal sterilization solution is heated to a temperature of 37° C. for 1 to 6 days.

18. The method of claim **14**, wherein the terminal sterilization solution is heated to a temperature of about 50° C. for 6 hours to 2 days.

19. The method of claim **1**, further comprising maintaining the glutaraldehyde solution in which the biological tissue is immersed at a temperature of about 30° C. to about 70° C. for about 1 hour to 6 months.

20. The method of claim **5**, further comprising maintaining the glutaraldehyde solution in which the biological tissue is immersed at a temperature of about 50° C. for about 7 to 10 days.

* * * * *

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that on October 18, 2022, the foregoing **CORRECTED OPENING BRIEF AND ADDENDUM OF APPELANTS EDWARDS LIFESCIENCES CORPORATION AND EDWARDS LIFESCIENCES LLC** was filed using the Court's CM/ECF system, which will send notice of such filing to all registered CM/ECF users..

DATED: November 7, 2022 By: */s/ Christy G. Lea*
Christy G. Lea

Attorney for Plaintiffs-Appellants
Edwards Lifesciences Corporation and
Edwards Lifesciences LLC

CERTIFICATE OF COMPLIANCE
UNDER FEDERAL RULES OF APPELLATE PROCEDURE
32(a)(7) AND FEDERAL CIRCUIT RULE 32

Counsel for Appellants Edwards Lifesciences Corporation and Edwards Lifesciences LLC certifies that the brief contained herein has a proportionally spaced 14-point typeface and contains 10,796 words, based on the "Word Count" feature of Word version Office365, including footnotes and endnotes. Pursuant to Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b), this word count does not include the words contained in the Certificate of Interest, Table of Contents, Table of Authorities, Abbreviations, and Statement of Related Cases.

DATED: November 7, 2022 By: */s/ Christy G. Lea*
Christy G. Lea

Attorney for Plaintiffs-Appellants
Edwards Lifesciences Corporation and
Edwards Lifesciences LLC

56590878